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(54) Title: INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit a prenyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting a prenyl-protein transferase and the prenylation of the oncogene protein Ras.

TITLE OF THE INVENTION
INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

DOMESTIC PRIORITY CLAIM

5   The priority of U.S. Provisional Application No. 60/062,660, filed October 8, 1997, is claimed.

BACKGROUND OF THE INVENTION

          The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras)
10   are part of a signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for
15   GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-
20   *ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.
          Ras must be localized to the plasma membrane for both
25   normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any
30   amino acid) (Willumsen *et al.*, *Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. Such enzymes
35   may be generally termed prenyl-protein transferase. (S. Clarke., *Ann.*

Rev. Biochem. 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins

5   such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to

10   those listed above.

       Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase

15   selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993) and G.L. James *et al.*, *Science*, *260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci*

20   *U.S.A.*, *91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

       Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and

25   compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX

30   box with a farnesyl group (Reiss *et al.*, *Cell*, *62*:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, *265*:14701-14704 (1990); Schafer *et al.*, *Science*, *249*:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, *87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in

35   cultured cells. However, direct inhibition of farnesyl-protein transferase

would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

5   Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for

10   protein prenylation. (Schaber et al., ibid; Reiss et. al., ibid; Reiss et al., PNAS, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl et al., Science,

15   260:1934-1937 (1993); Graham, et al., J. Med. Chem., 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics,

20   pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of

25   arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have

30   also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It is, therefore, an object of this invention to develop compounds that inhibit prenyl-protein transferase and thus, the post-translational isoprenylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the

compounds of this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises small molecule phenyl-containing compounds which inhibit a prenyl-protein transferase. Further contained in this invention are chemotherapeutic compositions containing these prenyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formula A:

$$(R^{13})_s - W - A^4 - (C(R^{1c})_2)_m$$

$$\left(R^3\right)_r \underset{R^2}{\bigcirc} - A^1(C(R^{1a})_2)_n A^2(C(R^{1a})_2)_n - X - (C(R^{1b})_2)_p A^3(C(R^{1b})_2)_p - Y \underset{R^4}{\overset{R^5}{<}}$$

$$\left(R^6\right)_t$$

A
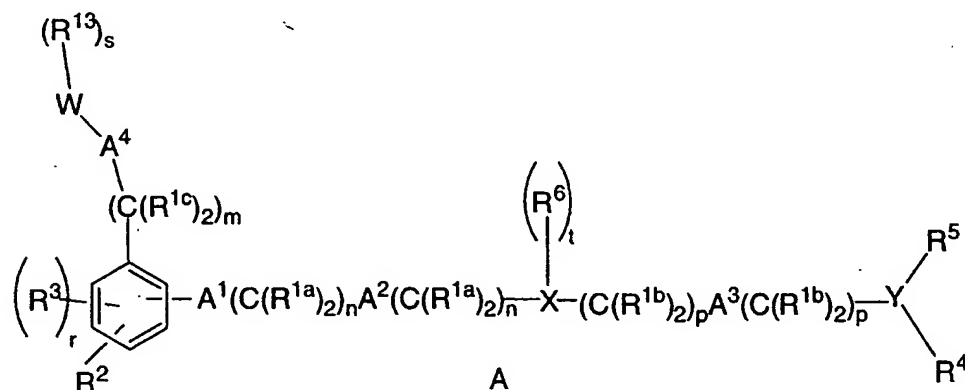
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of prenyl-protein transferase and the prenylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of prenyl-protein transferase are illustrated by the formula A:

$$\begin{array}{c} (R^{13})_s \\ | \\ W \\ \backslash \\ A^4 \\ | \\ (C(R^{1c})_2)_m \\ | \end{array}$$

$$\left(R^3\right)_r \!\!-\!\! \boxed{} \!\!-\!\! A^1(C(R^{1a})_2)_n A^2(C(R^{1a})_2)_{\overline{n}} \!\! \overset{\displaystyle (R^6)_t}{\underset{|}{X}} \!\!-\!\! (C(R^{1b})_2)_p A^3(C(R^{1b})_2)_{\overline{p}} \!\! Y \!\! \overset{R^5}{\underset{R^4}{<}}$$

$$R^2$$

A

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

    a)   hydrogen,

    b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

    a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

    f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

    h) N_3,

    i) $R^9S(O)_q$,

    j) $R^8HC=CH$-,

k) $R^8C\equiv C$-, and

l) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl,

N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl,

unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-,

C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8,

-$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

-$(C_1$-C_6 alkyl)$C(O)R^8$, -$CH=CH$-R^8 and $\underset{\underset{\textstyle OH}{|}}{-C}=\underset{\underset{\textstyle H}{|}}{C}-R^8$;

R^6 is independently selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O-,

i) N_3,

j) $R^9S(O)_q$-,

k)   -$HC=CH_2$,

l)   -$C\equiv CH$,

m) CF_3

n) $R^8O(C=O)$-, and

o) $R^8(O=C)O$-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, -(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)OC(O)(C_1-C_6 alkyl), -(C_1-C_6 alkyl)N(R^8)$_2$, and -(C_1-C_6 alkyl)NHC(O)(C_1-C_6 alkyl)R^8;

A^1, A^2 and A^3 are independently selected from:

- a)   a bond,
- b)   -HC=CH-,
- c)   -C≡C-,
- d)   -O-,
- e)   -(C=O)-,
- f)   -O(C=O)-,
- g)   -(C=O)O-,
- h)   -NR^8-,
- i)   -C(O)N(R^8)-,
- j)   -N(R^8)C(O)-,
- k)   -NHC(O)NH-,
- l)   -S(O)$_q$-,
- m)   -S(O)$_q$NH-, and
- n)   -NHS(O)$_q$-;

A^4 is selected from a bond, C(O), C=CH_2, or spiro C_3-C_6 cycloalkyl;

W is selected from:

- a)   hydrogen,
- b)   heterocycle, and
- c)   aryl;

X is selected from:

- a)   aryl,

b)   cycloalkyl,

c)   heterocycle, and

d)   a bond;

5   Y is selected from:

a)   aryl, unsubstituted or substituted

b)   heterocycle, unsubstituted or substituted, and

c)   cycloalkyl;

10   m is   0, 1, 2, 3 or 4;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

q is   0, 1 or 2;

r is   0, 1, 2 or 3;

15   s is   0, 1, 2, 3 or 4; and;

t is   0, 1, 2 or 3;

provided that

$$-\xi-A^1(C(R^{1a})_2)_n A^2(C(R^{1a})_2)_{\overline{n}} \overset{\overset{\displaystyle\left(R^6\right)_t}{|}}{X} -(C(R^{1b})_2)_p A^3(C(R^{1b})_2)_{\overline{p}}\xi\cdot$$

20   is not a bond;

or the pharmaceutically acceptable salts thereof.

In a further embodiment of this invention, the inhibitors of

25   a prenyl-protein transferase are illustrated by the formula A:

$$\text{(R}^{13}\text{)}_s$$

$$\text{W}$$

$$\text{A}^4$$

$$\text{(C(R}^{1c}\text{)}_2\text{)}_m$$

$$\left(\text{R}^3\right)_r \underset{\text{R}^2}{-} \overset{}{\bigcirc} - \text{A}^1\text{(C(R}^{1a}\text{)}_2\text{)}_n\text{A}^2\text{(C(R}^{1a}\text{)}_2\text{)}_n - \text{X} - \text{(C(R}^{1b}\text{)}_2\text{)}_p\text{A}^3\text{(C(R}^{1b}\text{)}_2\text{)}_p - \text{Y} \underset{\text{R}^4}{\overset{\text{R}^5}{<}}$$

$$\left(\text{R}^6\right)_t$$

A

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

5   a)   hydrogen,

      b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

10   c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

15 R^2 is selected from:

      a)   hydrogen,

      b)   CN,

      c) NO_2,

      d)   halogen,

20   e)   aryl, unsubstituted or substituted

      f)   heteroaryl, unsubstituted or substituted

      g) C_1-C_6 alkyl, unsubstituted or substituted

      h) N_3,

      i) $R^9S(O)_q$,

25   j) $R^8HC=C$-,

k) $R^8C \equiv C-$, and

l) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $-C \equiv CH$, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, $-C(O)R^8$, $-O(C_1-C_6$ alkyl$)OR^8$, $-NHC(O)R^8$, aralkyl, heteroaralkyl, $-(C_1-C_6$ alkyl$)OR^8$,

$$-\underset{\underset{OH}{|}}{C}=\underset{\underset{H}{|}}{C}-R^8$$

$-(C_1-C_6$ alkyl$)C(O)R^8$, $-CH=CH-R^8$ and   ;

R^6 is independently selected from:

a) hydrogen,

b) CN,

c) NO_2,

d) halogen,

e) aryl, unsubstituted or substituted,

f) heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O-, unsubstituted or substituted,

i) N_3,

j) $R^9S(O)_q-$,

k) $-HC=CH_2$,

l) $-C \equiv CH$,

m) CF_3

n) $R^8O(C=O)-$, and

o) $R^8 (O=C)O-$;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and
unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted
or substituted aryl, unsubstituted or substituted heterocycle,
-(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)$OC(O)(C_1$-C_6 alkyl), -(C_1-C_6
alkyl)$N(R^8)_2$, and -(C_1-C_6 alkyl)$NHC(O)(C_1$-C_6 alkyl)R^8;

A^1, A^2 and A^3 are independently selected from:

a)	a bond,	
b)	-HC=CH-,	
c)	-C≡C-,	
d)	-O-,	
e)	-(C=O)-,	
f)	-O(C=O)-,	
g)	-(C=O)O-,	
h)	-NR^8-,	
i)	-$C(O)N(R^8)$-,	
j)	-$N(R^8)C(O)$-,	
k)	-NHC(O)NH-,	
l)	-$S(O)_q$-,	
m)	-$S(O)_q$NH-, and	
n)	-$NHS(O)_q$-;	

A^4 is selected from a bond, C(O), C=CH_2, or spiro C_3-C_6 cycloalkyl;

W is selected from:

a)   heterocycle, and
b)   aryl;

X is selected from:

a)   aryl,
b)   cycloalkyl,

　　　　　　　c)　　heterocycle, and
　　　　　　　d)　　a bond;

　　　Y is selected from:
5　　　　　　a)　　aryl,
　　　　　　　b)　　heterocycle, and
　　　　　　　c)　　cycloalkyl;

　　　m is　0, 1, 2, 3 or 4;
10　　n is　0, 1, 2, 3 or 4;
　　　p is　0, 1, 2, 3 or 4;
　　　q is　0, 1 or 2;
　　　r is　1 or 2;
　　　s is　0, 1, 2, 3 or 4; and
15　　t is　0, 1, 2 or 3;

　　　provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_{\overline{n}}\overset{\displaystyle\left(R^6\right)_t}{X}-(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_{\overline{p}}\xi-$$

　　　is not a bond;
20

　　　or the pharmaceutically acceptable salts thereof.

　　　　　In another embodiment of the instant invention, the
　　　inhibitors of a prenyl-protein transferase are illustrated by formula B:

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

    a)   hydrogen,

    b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

    a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

    f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

    h) N_3,

    i) $R^9S(O)_q$,

    j) $R^8HC=CH$-,

    k) $R^8C\equiv C$-, and

l) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C-$, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, $-C(O)R^8$, $-O(C_1$-C_6 alkyl)OR^8, $-NHC(O)R^8$, aralkyl, heteroaralkyl, $-(C_1$-C_6 alkyl)OR^8,

$-(C_1$-C_6 alkyl)$C(O)R^8$, $-CH=CH-R^8$ and

$$-\underset{\underset{OH}{|}}{C}=\underset{H}{C}-R^8 \ ;$$

R^6 is independently selected from:

a)   hydrogen,
b)   CN,
c) NO_2,
d)   halogen,
e)   aryl, unsubstituted or substituted,
f)   heteroaryl, unsubstituted or substituted,
g) C_1-C_6 alkyl, unsubstituted or substituted,
h) R^8O-,
i) N_3,
j) $R^9S(O)_q-$,
k) $-HC=CH_2$,
l) $-C\equiv CH$,
m) CF_3
n) $R^8O(C=O)-$, and
o) $R^8 (O=C)O-$;

R^8 is independently selected from
hydrogen, unsubstituted or substituted C_1-C_6 alkyl, cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and
unsubstituted or substituted aryl;

R^{13} is independently selected from

5   H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted
or substituted aryl, unsubstituted or substituted heterocycle,
$-(C_1$-C_6 alkyl)OR^8, $-(C_1$-C_6 alkyl)$OC(O)(C_1$-C_6 alkyl), $-(C_1$-C_6
alkyl)$N(R^8)_2$, and $-(C_1$-C_6 alkyl)$NHC(O)(C_1$-C_6 alkyl)R^8;

10   A^1, A^2 and A^3 are independently selected from:

             a)   a bond,
             b)   -HC=CH-,
             c) $-C{\equiv}C$-,
             d)   -O-,
15   e)   -(C=O)-,
             f)   -O(C=O)-,
             g)   -(C=O)O-,
             h) $-NR^8$-,
             i) $-C(O)N(R^8)$-,
20   j) $-N(R^8)C(O)$-,
             k)   -NHC(O)NH-,
             l) $-S(O)_q$-,
             m) $-S(O)_qNH$-, and
             n) $-NHS(O)_q$-;

25

A^4 is selected from a bond, C(O), $C=CH_2$, or spiro C_3-C_6 cycloalkyl;

W is selected from:

             a)   heterocycle, and
30   b)   aryl;

X is selected from:

             a)   aryl,
             b)   cycloalkyl,

c)   heterocycle, and
d)   a bond;

m is 0, 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2;
s is 0, 1, 2, 3 or 4; and
t is 0, 1, 2, or 3;

provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_{\overline{n}}\overset{\displaystyle (R^6)_t}{\overset{|}{X}}-(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_{\overline{p}}\xi-$$
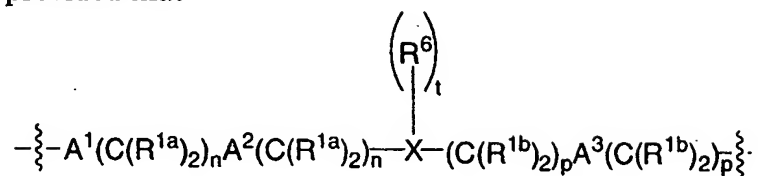
is not a bond;

or the pharmaceutically acceptable salts thereof.

In further embodiment of the instant invention, the inhibitors of a prenyl-protein transferase are illustrated by formula B:

B

wherein:
R^{1a}, R^{1b} and R^{1c} are independently selected from:

- 16 -

     a)   hydrogen,

     b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;
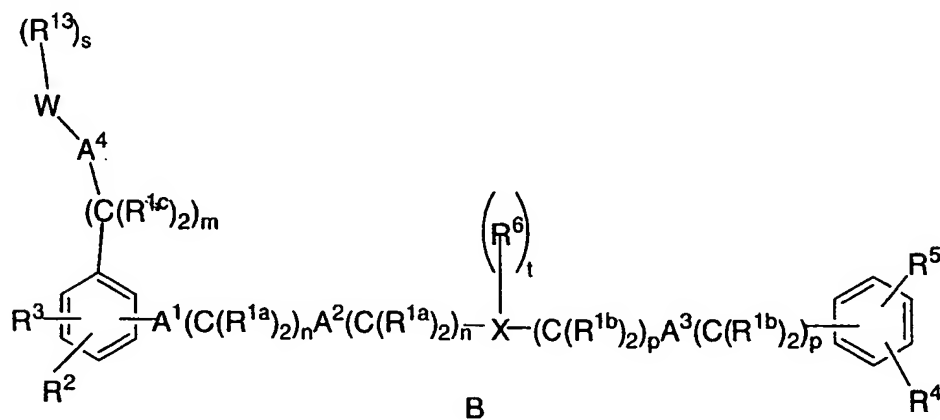
     c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

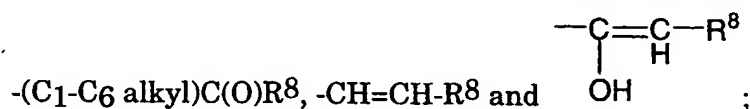R^2 is selected from:

     a)   hydrogen,

     b)   CN,

     c) NO_2,

     d)   halogen,

     e)   aryl, unsubstituted or substituted

     f)   heteroaryl, unsubstituted or substituted

     g) C_1-C_6 alkyl, unsubstituted or substituted

     h) N_3,

     i) $R^9S(O)_q$,

     j) $R^8HC=CH$-,

     k) $R^8C\equiv C$, and

     l) OR^8;

R^3, R^4 and R^5 are independently selected from:

     H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8, -$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

     -$(C_1$-C_6 alkyl)$C(O)R^8$, -$CH=CH$-R^8 and $-\overset{}{\underset{OH}{C}}=\overset{}{\underset{H}{C}}-R^8$;

R^6 is independently selected from:

	a)	hydrogen,
	b)	CN,
	c)	NO_2,
	d)	halogen,
5	e)	aryl, unsubstituted or substituted,
	f)	heteroaryl, unsubstituted or substituted,
	g)	C_1-C_6 alkyl, unsubstituted or substituted,
	h)	R^8O-,
	i)	N_3,
10	j)	$R^9S(O)_q$-,
	k)	-HC=CH$_2$,
	l)	-C≡CH,
	m)	CF_3
	n)	$R^8O(C=O)$-, and
15	o)	$R^8 (O=C)O$-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

20

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and

unsubstituted or substituted aryl;

25   R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted

or substituted aryl, unsubstituted or substituted heterocycle,

-(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)OC(O)(C_1-C_6 alkyl), -(C_1-C_6

alkyl)N(R^8)$_2$, and -(C_1-C_6 alkyl)NHC(O)(C_1-C_6 alkyl)R^8;

30

A^1 is selected from:

	a)	a bond,
	b)	-O-,
	c)	-(C=O)-,
35	d)	-NR^8-,

e)   -C(O)N(R8)-, and

f)   -S(O)q-;

A2 and A3 are independently selected from:

5   a)   a bond,

b)   -HC=CH-,

c)   -C≡C-,

d)   -O-,

e)   -(C=O)-,

10   f)   -O(C=O)-,

g)   -(C=O)O-,

h)   -NR8-,

i)   -C(O)N(R8)-,

j)   -N(R8)C(O)-,

15   k)   -NHC(O)NH-,

l)   -S(O)q-,

m)   -S(O)qNH-, and

n)   -NHS(O)q-;

20   A4 is selected from a bond, C(O), C=CH2, or spiro C3-C6 cycloalkyl;
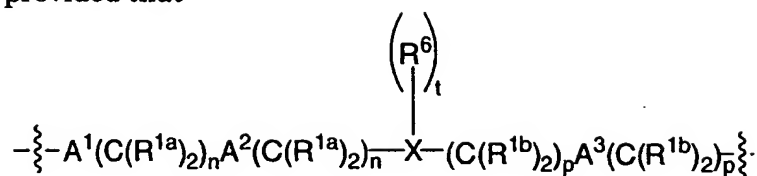
W is a heterocycle,

X is selected from:

25   a)   aryl,

b)   heterocycle, and

c)   a bond;

m is   0, 1, 2, 3 or 4;

30   n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

q is   0, 1 or 2;

s is   0, 1, 2, 3 or 4; and

t is   0, 1, 2 or 3;

provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_{\overline{n}}X-(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_{\overline{p}}\xi \cdot$$
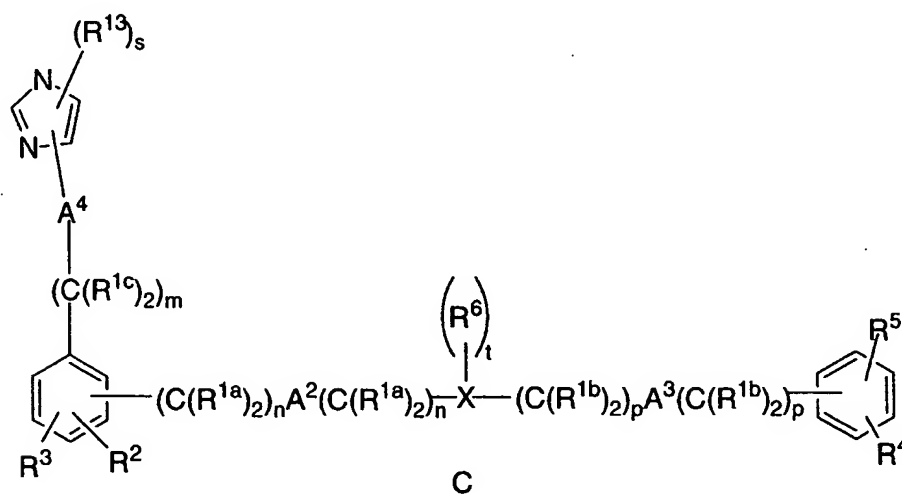
with $\left(R^6\right)_t$ above X

is not a bond;

or the pharmaceutically acceptable salts thereof.

In another embodiment of the instant invention, the inhibitors of a prenyl-protein transferase are illustrated by the formula C:

C

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

a)   hydrogen,

b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

-20-

c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted

f)   heteroaryl, unsubstituted or substituted

g) C_1-C_6 alkyl, unsubstituted or substituted

h) $R^9S(O)_q$, and

i) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl$)OR^8$, -$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl$)OR^8$,

$$-\overset{\displaystyle |}{\underset{\displaystyle OH}{C}}=\overset{\displaystyle H}{C}-R^8$$

-$(C_1$-C_6 alkyl$)C(O)R^8$, -$CH=CH$-R^8 and   ;

R^6 is independently selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O-,

i) N_3,

j) $R^9S(O)_q$-,

k) CF_3

l) $R^8O(C=O)$-, and

m) $R^8(O=C)O$-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and

unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted

or substituted aryl, unsubstituted or substituted heterocycle,
-$(C_1$-C_6 alkyl)OR^8, -$(C_1$-C_6 alkyl)$OC(O)(C_1$-C_6 alkyl), -$(C_1$-C_6
alkyl)$N(R^8)_2$, and -$(C_1$-C_6 alkyl)$NHC(O)(C_1$-C_6 alkyl)R^8;

A^2 is selected from:

a)   a bond,

b)   -HC=CH-,

c)   -C≡C-,

d)   -O-,

e)   -(C=O)-,

f)   -O(C=O)-,

g)   -(C=O)O-,

h)   -NR^8-,

i)   -$C(O)N(R^8)$-,

j)   -$N(R^8)C(O)$-,

k)   -NHC(O)NH-,

l)   -$S(O)_q$-,

m)   -$S(O)_qNH$-, and

n)   -NHS(O)$_q$-;

A^3 is selected from:

a)   a bond,
b)   -O-,
c)   -S(O)$_q$-,
d)   -S(O)$_q$NH-,
e)   -NR^8-,
f)   -(C=O)-,
g)   -(C=O)O-,
h)   -O(C=O)-,
i)   -C(O)N(R^8)-,
j)   -N(R^8)C(O)-, and
k)   -NHC(O)NH-;

A^4 is selected from a bond, C(O), C=CH$_2$, or spiro C$_3$-C$_6$ cycloalkyl;

X is selected from:

a)   aryl,
b)   heterocycle, and
c)   a bond;

m is   0, 1, 2, 3 or 4;
n is   0, 1, 2, 3 or 4;
p is   0, 1, 2, 3 or 4;
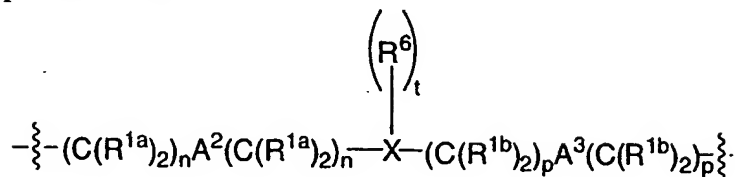q is   0, 1 or 2;
s is   0, 1, 2, 3 or 4; and
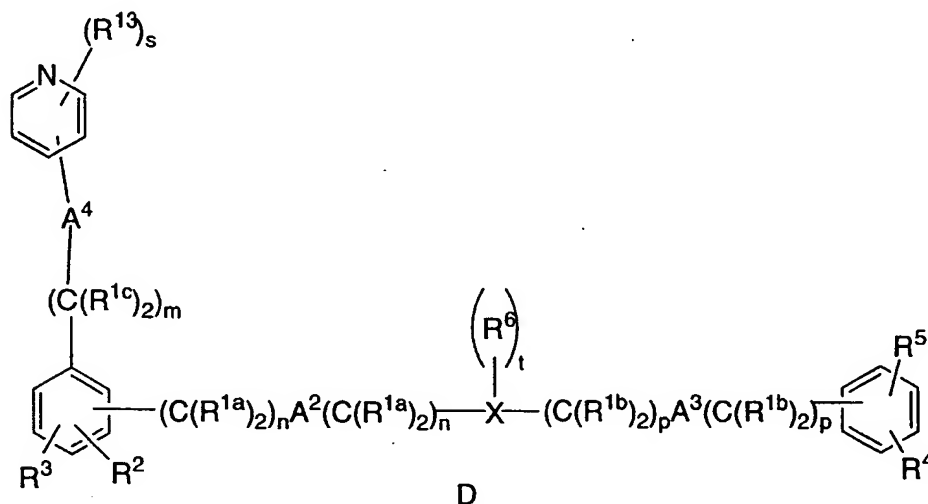t is   0, 1, 2 or 3;

provided that

$$-\xi-(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n-X-\overset{\left(\underset{\big|}{R^6}\right)_t}{}(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_p-\xi-$$

- 23 -

is not a bond;

or the pharmaceutically acceptable salts thereof.

In another embodiment of the instant invention, the inhibitors of a prenyl-protein transferase are illustrated by the formula D:

D

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

    a)   hydrogen,

    b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

    a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted

f)   heteroaryl, unsubstituted or substituted

g) C_1-C_6 alkyl, unsubstituted or substituted

h) $R^9S(O)_q$, and

i) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8, -$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

$$-\underset{\underset{OH}{|}}{C}=\underset{\underset{H}{|}}{C}-R^8$$

-$(C_1$-C_6 alkyl)$C(O)R^8$, -CH=CH-R^8 and   ;

R^6 is independently selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O-,

i) N_3,

j) $R^9S(O)_q$-,

k) CF_3

l) $R^8O(C=O)$-, and

m) $R^8(O=C)O$-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and

unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted

or substituted aryl, unsubstituted or substituted heterocycle,

-(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)$OC(O)(C_1$-C_6 alkyl), -(C_1-C_6

alkyl)$N(R^8)_2$, and -(C_1-C_6 alkyl)$NHC(O)(C_1$-C_6 alkyl)R^8;

A^2 is selected from:

a)   a bond,

b)   -HC=CH-,

c)   -C≡C-,

d)   -O-,

e)   -(C=O)-,

f)   -O(C=O)-,

g)   -(C=O)O-,

h)   -NR^8-,

i)   -$C(O)N(R^8)$-,

j)   -$N(R^8)C(O)$-,

k)   -NHC(O)NH-,

l)   -$S(O)_q$-,

m)   -$S(O)_q$NH-, and

n)   -$NHS(O)_q$-;

A^3 is selected from:

a)   a bond,

b)   -O-,

c)   -$S(O)_q$-,

d)   -$S(O)_q$NH-,

e)   -NR^8-,

f)   -(C=O)-,

g)   -(C=O)O-,

h)   -O(C=O)-,

i)   -C(O)N(R^8)-,

j)   -N(R^8)C(O)-, and

k)   -NHC(O)NH-;

A^4 is selected from a bond, C(O), C=CH$_2$, or spiro C$_3$-C$_6$ cycloalkyl;

X is selected from:

a)   aryl,

b)   heterocycle, and

c)   a bond;

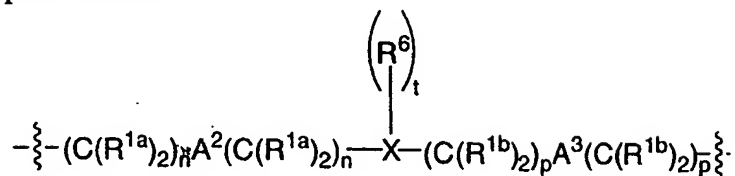m is   0, 1, 2, 3 or 4;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

q is   0, 1 or 2; and
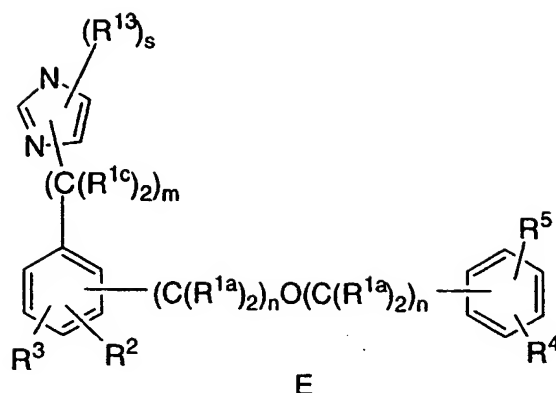
s is   0, 1, 2, 3 or 4; and

t is   0, 1, 2, or 3;

provided that

$$-\xi-(C(R^{1a})_2)_m A^2(C(R^{1a})_2)_n-X-(C(R^{1b})_2)_p A^3(C(R^{1b})_2)_p \xi-$$

with $\left(R^6\right)_t$

is not a bond;

or the pharmaceutically acceptable salts thereof.

In another embodiment of the instant invention, the inhibitors of a prenyl-protein transferase are illustrated by the formula E:

E

wherein:

R^{1a} and R^{1c} are independently selected from:

    a)   hydrogen,

5   b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl,

10   heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

15   a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

20   f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

    h) $R^9S(O)_q$, and

    i) OR^8;

25   R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl,
N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl,
unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-,
C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8,
-$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

-$(C_1$-C_6 alkyl)$C(O)R^8$, -CH=CH-R^8 and

$$-\underset{\underset{OH}{|}}{C}=\underset{H}{C}-R^8 ;$$

R^8 is independently selected from
hydrogen, unsubstituted or substituted C_1-C_6 alkyl,
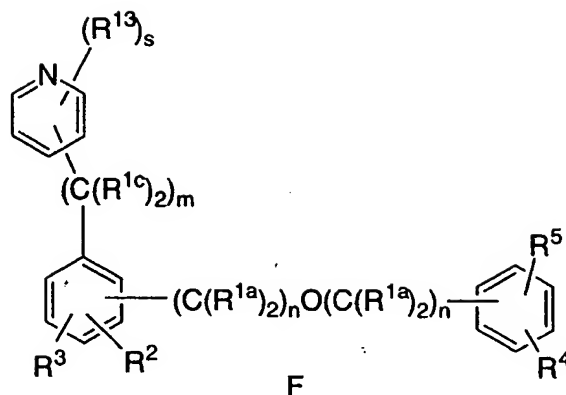cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from
H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and
unsubstituted or substituted aryl;

R^{13} is independently selected from
H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted
or substituted aryl, unsubstituted or substituted heterocycle,
-$(C_1$-C_6 alkyl)OR^8, -$(C_1$-C_6 alkyl)$OC(O)(C_1$-C_6 alkyl), -$(C_1$-C_6
alkyl)$N(R^8)_2$, and -$(C_1$-C_6 alkyl)$NHC(O)(C_1$-C_6 alkyl)R^8;

m is   0, 1, 2, 3 or 4;
n is   0, 1, 2, 3 or 4;
q is   0, 1 or 2; and
s is   0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In another embodiment of the instant invention, the
inhibitors of a prenyl-protein transferase are illustrated by the formula
F:

$$
\begin{array}{c}
(R^{13})_s \\
\text{N} \\
\text{(pyridine ring)} \\
(C(R^{1c})_2)_m \\
\text{(benzene ring)} \quad -(C(R^{1a})_2)_n O(C(R^{1a})_2)_n - \text{(benzene ring with } R^5, R^4) \\
R^3 \quad R^2 \\
F
\end{array}
$$

wherein:

R^{1a} and R^{1c} are independently selected from:

    a)   hydrogen,

5   b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl,

10   heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

    R^2 is selected from:

15   a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

20   f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

    h) $R^9S(O)_q$, and

    i) OR^8;

25   R^3, R^4 and R^5 are independently selected from:

H, CN, NO$_2$, halogen, unsubstituted or substituted C$_1$-C$_6$ alkyl,
N$_3$, R^{9}S(O)$_q$, HC≡C-, unsubstituted or substituted aryl,
unsubstituted or substituted heterocycle, CF$_3$, CF$_3$O-, CF$_3$CH$_2$O-,
C$_3$-C$_{10}$ cycloalkyl, OR^8, N(R^8)$_2$, -C(O)R^8, -O(C$_1$-C$_6$ alkyl)OR^8,
-NHC(O)R^8, aralkyl, heteroaralkyl, -(C$_1$-C$_6$ alkyl)OR^8,

$$-\overset{\underset{\displaystyle OH}{|}}{C}=\overset{\underset{\displaystyle H}{}}{C}-R^8$$

-(C$_1$-C$_6$ alkyl)C(O)R^8, -CH=CH-R^8 and ;

R^8 is independently selected from
 hydrogen, unsubstituted or substituted C$_1$-C$_6$ alkyl,
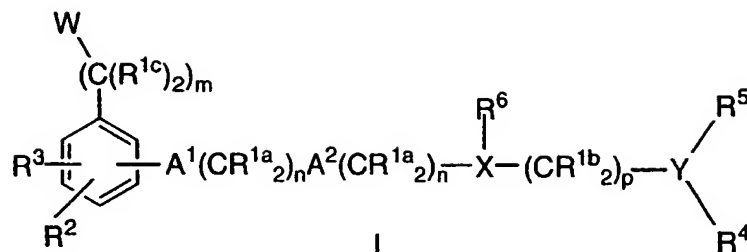 cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from
 H, unsubstituted or substituted C$_1$-C$_6$ alkyl, benzyl and
 unsubstituted or substituted aryl;

R^{13} is independently selected from
 H, unsubstituted or substituted C$_1$-C$_6$ alkyl, unsubstituted
 or substituted aryl, unsubstituted or substituted heterocycle,
 -(C$_1$-C$_6$ alkyl)OR^8, -(C$_1$-C$_6$ alkyl)OC(O)(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$
 alkyl)N(R^8)$_2$, and -(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8;

m is 0, 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
q is 0, 1 or 2; and
s is 0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In second embodiment of the instant invention, the
inhibitors of a prenyl-protein transferase are illustrated by the formula
I:

$$W$$
$$\setminus$$
$$(\overset{|}{\underset{|}{C}}(R^{1c})_2)_m$$

$$R^3 \overset{|}{\underset{|}{\parallel}} \quad A^1(CR^{1a}_2)_n A^2(CR^{1a}_2)_{\overline{n}} X-(CR^{1b}_2)_p - Y$$

with R^6, R^5, R^4 substituents and R^2

I

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

5   a)   hydrogen,

b)   unsubstituted or substituted aryl; unsubstituted or
substituted heterocycle; unsubstituted or substituted
heteroaryl; C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,
R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, or N_3;

10   c) C_1-C_6 alkyl, unsubstituted or substituted by aryl,
heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6
alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or
$R^8C(O)O$-;

15   R^2 is selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

20   e)   aryl,

f)   heteroaryl,

g) C_1-C_6 alkyl,

h) C_1-C_6 alkoxy,

i) N_3,

25   j) $R^9S(O)_q$,

k) $R^8C=C$, and

l) $R^8C\equiv C$;

R^3, R^4 and R^5 are independently selected from:

a)   H,

b)   CN,

c) NO_2,

d)   halogen,

5   e) C_1-C_6 alkyl,

f) C_1-C_6 alkoxy,

g) N_3,

h) $R^9S(O)_q$,

i)   -HC=CH_2,

10   j)   -C≡CH,

k)   aryl, unsubstituted or substituted,

l)   heterocycle, unsubstituted or substituted,

m) CF_3O-,

n) CF_3CH_2O-,

15   o) C_3-C_{10} cycloalkyl, and

p) CF_3;

R^6 is independently selected from:

a)   hydrogen,

20   b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

25   g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O,

i) N_3,

j) $R^9S(O)_q$,

k)   -HC=CH_2,

30   l)   -C≡CH,

m) CF_3

n) $R^8O(C=O)$,and

o) $R^8 (O=C)O$;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl, benzyl and aryl;

A^1 and A^2 are independently selected from:
  a) a bond,
  b) -HC=CH-,
  c) -C≡C-,
  d) O,
  e) $S(O)_q$,
  f) O(C=O),
  g) (O=C), and
  h) (C=O)O;

W is selected from:
  a)   hydrogen,
  b)   heterocycle, unsubstituted or substituted, and
  c)   aryl, unsubstituted or substituted;

X is selected from:
  a)   aryl,
  b)   heteroaryl,
  c)   cycloalkyl,
  d)   heterocycle, and
  e)   a bond;

Y is selected from:
  a)   aryl, unsubstituted or substituted,
  b)   heterocycle, unsubstituted or substituted, and
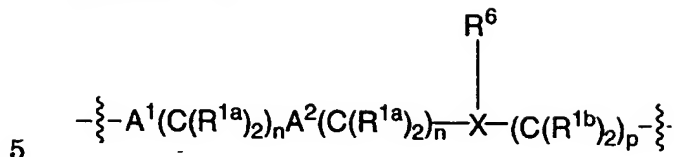 c)   heteroaryl, unsubstituted or substituted;

m is   0, 1, 2, 3 or 4;
n is   0, 1, 2, 3 or 4;

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p is   0, 1, 2, 3 or 4; and

q is   0, 1 or 2;

provided that

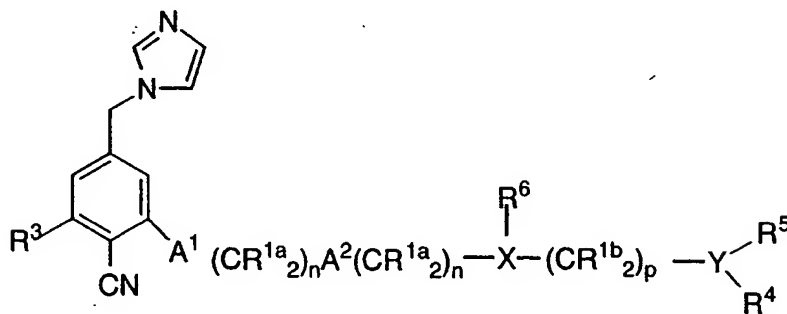$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n\overset{\overset{\textstyle R^6}{|}}{-}X-(C(R^{1b})_2)_p-\xi-$$

is not a bond;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula Ia:

Ia

wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:
    a)   hydrogen,
    b)   aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O- or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl,
        heterocycle, cycloalkyl, alkenyl, or R^8O-;

R^3 and R^4 are independently selected from hydrogen, F, Cl, Br, N_3,
        CN, C_1-C_6 alkyl, substituted or unsubstituted aryl and
        substituted or unsubstituted heterocycle;

R^5 is selected from:
        a) hydrogen, and
        b) C_1-C_6 alkyl substituted with hydrogen or a group selected
        from unsubstituted or substituted aryl, unsubstituted or
        substituted heterocyclic, unsubstituted or substituted C_3-
        C_{10} cycloalkyl, CF_3, NO_2, R^8O-, $R^9S(O)_q$-, $R^8C(O)$-,
        $R^8OC(O)$-, N_3, and CN;

R^6 is independently selected from:
        a)   hydrogen,
        b) C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, F, Cl, CN, NO_2, and
        c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-,
                $R^8C(O)$-, or $R^8OC(O)$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and
        aryl;

R^9 is independently selected from C_1-C_6 alkyl, benzyl and aryl;

A^1 and A^2 are independently selected from: a bond, -HC=CH-, -C≡C-, O,
        $S(O)_q$, O(C=O), and (O=C)O;

X is selected from:
        a)   aryl,
        b)   heteroaryl,
        c)   cycloalkyl,
        d)   heterocycle, and
        e)   a bond;

Y is selected from:

        a)   aryl,
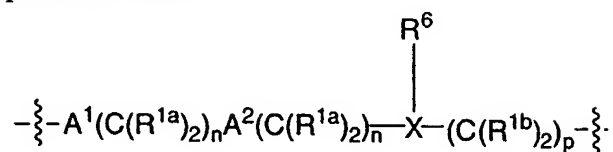
        b)   substituted aryl,

        c)   heterocycle, and

        d)   substituted heterocycle;

n is   0, 1, 2, 3 or 4;

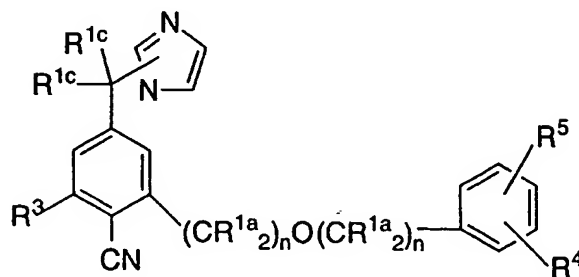p is   0, 1, 2, 3 or 4; and

q is   0, 1, or 2;

provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n\overset{\overset{\displaystyle R^6}{\displaystyle |}}{X}-(C(R^{1b})_2)_p-\xi-$$

is not a bond;

or the pharmaceutically acceptable salts thereof.

A further embodiment of the compounds of the instant invention is illustrated by Formula Ib:

Ib

wherein:

R^{1a} is selected from:

a)   hydrogen,

b)   unsubstituted or substituted aryl; unsubstituted or substituted heterocycle; unsubstituted or substituted heteroaryl; C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, or N_3;

c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or -$R^8C(O)O$-;

R^{1c} is independently selected from: H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R^3 is selected from hydrogen, F, Cl, Br, N_3, CN, C_1-C_6 alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^4 and R^5 are independently selected from:

a)   H,

b)   halogen,

c)   aryl, unsubstituted or substituted,

d)   heteroaryl, unsubstituted or substituted, and

e) C_1-C_6 alkyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl, benzyl and aryl;

n is independently selected from: 0, 1, 2, 3 or 4; and

q is   0, 1 or 2;

or the pharmaceutically acceptable salts thereof.

Specific examples of the compounds of the invention are:

3-(biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

5   3-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-ylmethylbenzonitrile

3-(biphenyl-3-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

10

2-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

1-*tert*-butoxycarbonyl-4-(3-chlorophenyl)-2(S)-[2-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)ethyl]piperazine

15

2-(3-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

20   2-(3-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(phenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

25

2-(3-chlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-chlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

30   2-(2,4-dichlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(benzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphenyl-2-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

35

2-(phenyl-4-butoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(phenyl-3-propoxy)-4-imidazol-1-ylmethyl-benzonitrile

5   2-(biphenyl-4-yl-2-ethoxy)-4-(1,2,4-triazol-1-yl)methyl-benzonitrile

2-(biphenyl-4-yl-2-ethoxy)-4-(2-methyl-imidazol-1-yl)methyl-benzonitrile

2-(biphenyl-4-yl-2-ethoxy)-4-benzimidazol-1-yl)methyl-benzonitrile

10

4-imidazol-1-ylmethyl-2-(naphthalen-2-yloxy)-benzonitrile

2-(3-cyanophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

15   2-(3-bromophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphen-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphen-4-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

20

2-(3-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

25   2-(3-trifluoromethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

30

2-(4-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

35   2-(2-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,5-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

5

2-(3,4-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,5-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

10   2-(1-naphthyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-fluorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

15

2-(3-t-butylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-[3-(N,N-diethylamino)phenoxy]-4-imidazol-1-ylmethyl-benzonitrile

20   2-(3-n-propylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,3-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,3-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

25

2-(3,4-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,5-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

30   2-(3,4-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-chloro-2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

35

2-(5-chloro-2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chloro-4,5-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

5   2-(5-hydroxymethyl-2-methoxyphenoxy)-4-imidazol-1-ylmethyl-
       benzonitrile

4-imidazol-1-ylmethyl-2-(3-phenylamino-phenoxy)-benzonitrile

10   4-imidazol-1-ylmethyl-2-[3-(2-methylphenylamino)-phenoxy]-benzonitrile

4-imidazol-1-ylmethyl-2-(3-phenoxy-phenoxy)-benzonitrile

2-(2-benzoyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
15
1-(5-chloro-2-methoxy-phenyl)-3-[3-(2-cyano-5-imidazol-1-
ylmethyl-phenoxy)-phenyl]-urea

1-(2,5-dimethoxy-phenyl)-3-[3-(2-cyano-5-imidazol-1-
20   ylmethyl-phenoxy)-phenyl]-urea

2-(3-benzyloxy-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-benzyloxy-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
25
2-(2-benzyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-ethynyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

30   2-(4-acetyl-3-methyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(1H-indazol-6-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(5,6,7,8-tetrahydro-naphthalen-1-yloxy)-
35   benzonitrile

- 42 -

4-imidazol-1-ylmethyl-2-(8-oxo-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-benzonitrile

5   4-imidazol-1-ylmethyl-2-(1*H*-indol-7-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(3-oxo-indan-4-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(1*H*-indol-4-yloxy)-benzonitrile

10

2-[3-(2-hydroxy-ethoxy)-phenoxy]-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(4-imidazol-1-yl-phenoxy)-benzonitrile

15   4'-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-biphenyl-4-carbonitrile

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-acetamide

4-imidazol-1-ylmethyl-2-(9-oxo-9*H*-fluoren-4-yloxy)-benzonitrile

20

3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*phenyl-benzamide

3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-ethyl-*N*-phenyl-benzamide

25   3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-cyclopropylmethyl-*N*-phenyl-benzamide

2-(5-chloro-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

30   *N*-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-benzenesulfonamide

4-imidazol-1-ylmethyl-2-(indan-5-yloxy)-benzonitrile

35   3-(9*H*-carbazol-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-
benzonitrile

5 4-imidazol-1-ylmethyl-2-(2-methoxy-4-propenyl-phenoxy)-benzonitrile

4-imidazol-1-ylmethyl-2-[4-(3-oxo-butyl)-phenoxy]-benzonitrile

2-(3-chlorophenoxy)-5-imidazol-1-ylmethyl-benzonitrile

10

2-(4-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,5-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

15 2-(pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-chlorophenoxy)-5-(4-phenyl-imidazol-1-ylmethyl)-benzonitrile

20

2-(biphen-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

25 2-(2-chloro-4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(naphthalen-2-ylsulfanyl)-benzonitrile

30

2-(2,4-dichlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dichloro-benzenesulfinyl)-4-imidazol-1-ylmethyl-benzonitrile

35 2-(2,4-dichloro-benzenesulfonyl)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-methyl-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dimethyl-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

5

2-(4-chloro-2-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chlorophenoxy)-4-(5-methyl-imidazol-1-ylmethyl)-benzonitrile

10   2-(2-chlorophenoxy)-4-(4-methyl-imidazol-1-ylmethyl)-benzonitrile

2-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-4-imidazol-1-ylmethyl-
benzonitrile

15   2-(2,4-dichlorophenoxy)-4-(2-methyl-imidazol-1-ylmethyl)-benzonitrile

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-benzamide

2-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-*N*-phenyl-
20   acetamide

4-imidazol-1-ylmethyl-2-(quinolin-6-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-benzonitrile

25

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-2-phenyl-
acetamide

5-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-cyclohexyl-nicotinamide

30

N-(3-chloro-phenyl)-5-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-
nicotinamide

2-(2,3-dimethoxyphenoxy)-4-(2,4-dimethyl-imidazol-1-ylmethyl)-
35   benzonitrile

4-(2-methyl-imidazol-1-ylmethyl)-2-(naphthalen-2-yloxy)-benzonitrile

4-(1-imidazol-1-yl-1-methyl-ethyl)-2-(naphthalen-2-yloxy)-benzonitrile

5

1-[4-iodo-3-(naphthalen-2-yloxy)-benzyl]-1*H*-imidazole

acetic acid 3-[3-(2-chloro-phenoxy)-4-cyano-benzyl]-3H-imidazol-4-ylmethyl ester

10

2-(2-chloro-phenoxy)-4-(5-hydroxymethyl-imidazol-1-ylmethyl)-benzonitrile

4-(5-aminomethyl-imidazol-1-ylmethyl)-2-(2-chloro-phenoxy)-
15   benzonitrile

N-{3-[4-cyano-3-(2,3-dimethoxy-phenoxy)-benzyl]-3H-imidazol-4-ylmethyl}-2-cyclohexyl-acetamide

20   2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-benzonitrile

2-(3-chloro-phenoxy)-4-[1-(4-chloro-phenyl)-2-hydroxy-1-imidazol-1-yl-ethyl]-benzonitrile

25

2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-hydroxy-(3*H*-imidazol-4-yl)-methyl]-benzonitrile

2-(2,4-dichloro-phenylsulfanyl)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-
30   ylmethyl]-benzonitrile

2-(2,4-dichloro-phenoxy)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-ylmethyl]-benzonitrile

4-[hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-2-(naphthalen-2-yloxy)-benzonitrile

4-[amino-(3-methyl-3*H*-imidazol-4-yl)-methyl]-2-(naphthalen-2-yloxy)-
5   benzonitrile

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-benzonitrile

10   4-[1-amino-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-benzonitrile hydrochloride

3-{2-cyano-5-[1-amino-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-ethyl-*N*-phenyl-benzamide
15

3-{2-cyano-5-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-ethyl-*N*-phenyl-benzamide

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(3-phenylamino-
20   phenoxy)-benzonitrile

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(3-phenoxy-phenoxy)-benzonitrile

25   2-(3-benzoyl-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-benzonitrile

2-(3-*tert*-butyl-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-benzonitrile
30

2-(3-diethylamino-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-benzonitrile

2-(5-chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethoxy)-4-imidazol-1-
ylmethyl-benzonitrile

4-Imidazol-1-ylmethyl-2-[2-(2-oxo-2H-pyridin-1-yl)-phenoxy]-benzonitrile

5

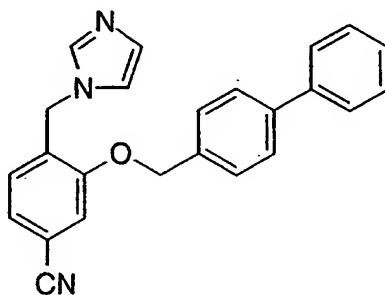4-Imidazol-1-ylmethyl-2-[3-(2-oxo-2H- pyridin-1-yl)-phenoxy]-benzonitrile

4-Imidazol-1-ylmethyl-2-[4-(2-oxo-2H- pyridin-1-yl)-phenoxy]-benzonitrile
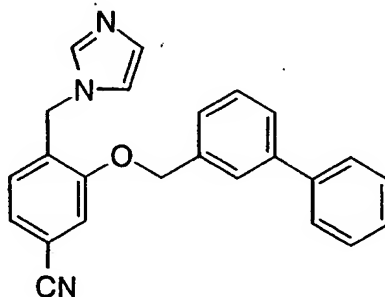
10

or the pharmaceutically acceptable salts thereof.

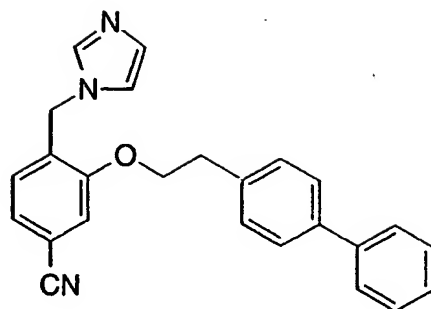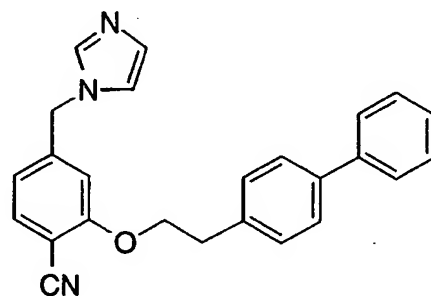The preferred compounds of the instant invention are:

15

3-(Biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

20   3-(Biphenyl-3-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

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3-(Biphenyl-4-yl-2-ethoxy)-4-imidazol-1-ylmethylbenzonitrile.

5   2-(Biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile
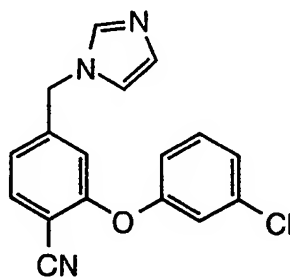
2-(3-Chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile
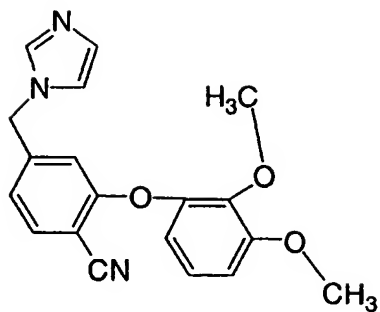
4-Imidazol-1-ylmethyl-2-(naphthalen-2-yloxy)-benzonitrile

5
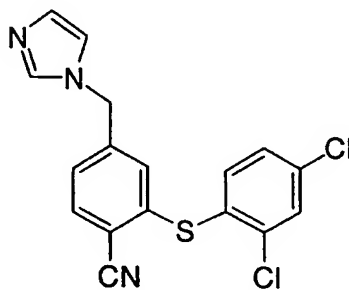
2-(2,4-Dichlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile

10

3-(2-Cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-ethyl-*N*-phenyl-benzamide

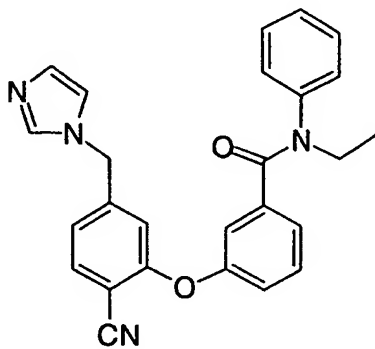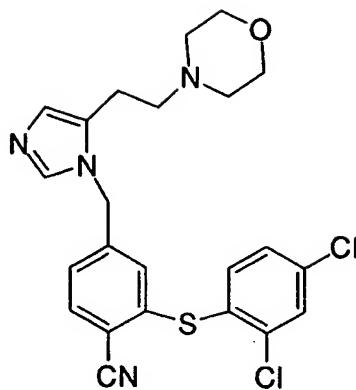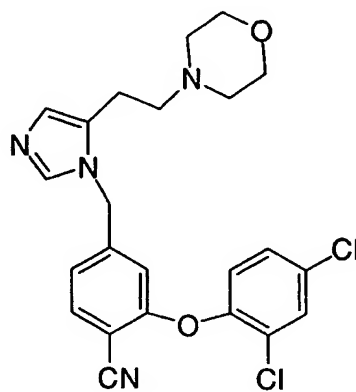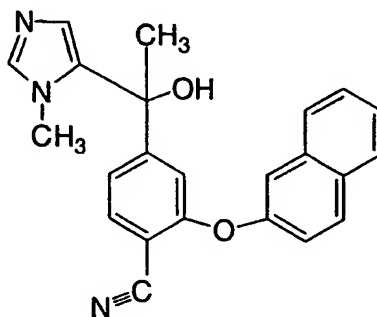2-(2,4-dichloro-phenylsulfanyl)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-ylmethyl]-benzonitrile

2-(2,4-dichloro-phenoxy)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-ylmethyl]-benzonitrile

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-
benzonitrile
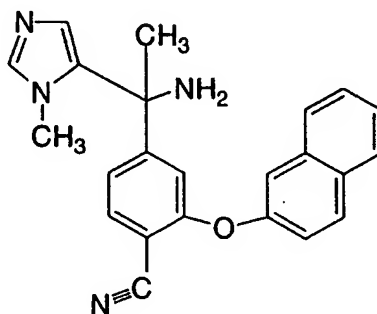
5   4-[1-amino-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-
benzonitrile

or a pharmaceutically acceptable salt thereof.

10   The compounds of the present invention may have
asymmetric centers and occur as racemates, racemic mixtures, and as
individual diastereomers, with all possible isomers, including optical
isomers, being included in the present invention. When any variable,
substituent or term (e.g. aryl, heterocycle, R^{1a}, R^2, n, p, etc.) occurs
15   more than one time in a formula or generic structure, its definition at
each occurrence is independent of the definition at every other
occurrence. Also, combinations of substituents/or variables are
permissible only if such combinations result in stable compounds.
          As used herein, "alkyl" is intended to include both
20   branched and straight-chain saturated aliphatic hydrocarbon groups
having 1 to 6 carbon atoms, unless otherwise specified; "alkoxy"
represents an alkyl group having 1 to 4 carbon atoms, unless otherwise
indicated, attached through an oxygen bridge. "Halogen" or "halo" as
used herein means fluoro, chloro, bromo and iodo.
25   As used herein, "aryl" is intended to mean any stable
monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each
ring, wherein at least one ring is aromatic. Examples of such aryl

elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, indanonyl, biphenyl, tetralinyl, tetralonyl, fluorenonyl, phenanthryl, anthryl or acenaphthyl.

As used herein, "aralkyl" is intended to mean an aryl moiety, as defined above, attached through a C_1-C_6 alkyl linker, where alkyl is defined above. Examples of aralkyls inlcude, but are not limited to, benzyl, naphthylmethyl and phenylpropyl.

As used herein, "heteroaralkyl" is intended to mean a heteroaryl moiety, as defined below, attached through a C_1-C_6 alkyl linker, where alkyl is defined above. Examples of heteroaralkyls include, but are not limited to, 2-pyridylmethyl, 2-imidazolylethyl, 2-quinolinylmethyl, 2-imidazolylmethyl and the like.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, chromanyl, cinnolinyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinolinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl,

thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl and triazolyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein, the terms "substituted C_1-C_6 alkyl" and "substituted C_1-C_6 alkoxy" are intended to include the branch or straight-chain alkyl group of the specified number of carbon atoms, wherein the carbon atoms may be substituted with F, Cl, Br, CF_3, N_3, NO_2, NH_2, oxo, -OH, -O(C_1-C_6 alkyl), $S(O)_{0-2}$, (C_1-C_6 alkyl)$S(O)_{0-2}$-, (C_1-C_6 alkyl)$S(O)_{0-2}$(C_1-C_6 alkyl)-, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -C(O)NH, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, -O(C_1-C_6 alkyl)CF_3, (C_1-C_6 alkyl)OC(O)-, (C_1-C_6 alkyl)O(C_1-C_6 alkyl)-, (C_1-C_6 alkyl)$C(O)_2$(C_1-C_6 alkyl)-, (C_1-C_6 alkyl)OC(O)NH-, aryl, benzyl, heterocycle, aralkyl, heteroaralkyl, halo-aryl, halo-benzyl, halo-heterocycle, cyano-aryl, cyano-benzyl and cyano-heterocycle.

As used herein, the terms "substituted aryl", "substituted heteroaryl", "substituted aralkyl" and "substituted heteroaralkyl" are intended to include the cyclic group containing from 1 to 3 substitutents in addition to the point of attachment to the rest of the compound. Such substitutents are preferably selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, N(C_1-C_6 alkyl)$_2$, NO_2, CN, N_3, C_1-C_{20} alkyl, C_1-C_6 alkoxy, -

OH, -O(C_1-C_6 alkyl), S(O)$_{0-2}$, (C_1-C_6 alkyl)S(O)$_{0-2}$-, (C_1-C_6 alkyl)S(O)$_{0-2}$(C_1-C_6 alkyl)-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, (C_1-C_6 alkyl)O(C_1-C_6 alkyl)-, (C_1-C_6 alkyl)C(O)$_2$(C_1-C_6 alkyl)-, (C_1-C_6 alkyl)OC(O)NH-, aryl, aralkyl,

5   heteroaryl, heteroaralkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heteroaralkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heteroaralkyl.

Examples of "spiro C_1-C_6 cycloalkyl" include:
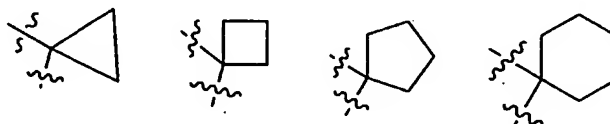
10   Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms or heteroatom.

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, unsubstituted or substituted aryl or unsubstituted or
15   substituted C_1-C_6 alkyl.

Preferably, R^{1c} is selected from hydrogen, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, -OR^8, -N(R^8)$_2$ and unsubstituted or substituted C_1-C_6 alkyl.

Preferably, R^2 is H, CN or halo. Most preferably, R^2 is CN.
20   Preferably, R^3 is selected from hydrogen, halo, CN, NO_2, and unsubstituted or substituted C_1-C_6 alkyl.

Preferably, R^4 and R^5 are independently selected from hydrogen, halo, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, N_3,
25   -C(O)R^8, -O(C_1-C_6 alkyl)OR^8, and -(C_1-C_6 alkyl)OR^8.

Preferably, R^6 is selected from: hydrogen, F, Cl, Br, CN, NO_2, R^8OC(O)-, N_3, and C_1-C_6 alkyl.

Preferably, R^{13} is selected from hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, -(C_1-C_6
30   alkyl)OR^8, -(C_1-C_6 alkyl)OC(O)(C_1-C_6 alkyl), -(C_1-C_6 alkyl)N(R^8)$_2$, and

-(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8. More preferably, R^{13} is substituted C$_1$-C$_6$ alkyl, unsubstituted or substituted aryl, -(C$_1$-C$_6$ alkyl)OR^8, -(C$_1$-C$_6$ alkyl)OC(O)(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$ alkyl)N(R^8)$_2$, and -(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8.

5   Preferably, A^1 and A^2 are independently selected from: a bond, O and S(O)$_q$. More preferably, A^1 is a bond and A^2 is selected from O and S(O)$_q$.

Preferably, A^3 is selected from a bond, O, -NR^8, C(O), -S(O)$_q$, -C(O)N(R^8), -N(R^8)C(O), -S(O)$_q$NH, -NHS(O)$_q$, or -NHC(O)NH.

10   Preferably A^4 is selected from a bond, C=CH$_2$, or spiro C$_3$-C$_6$ cycloalkyl. Most preferably, A^4 is a bond.

Preferably, W is a heterocycle, selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and

15   thienyl. Most preferably, W is imidazolyl or pyridyl.

Preferably, X is selected from a bond, aryl and heterocycle.

Preferably, Y is selected from an unsubstituted or substituted aryl or an unsubstituted or substituted heterocycle. More preferably, Y is selected from phenyl, furyl, thienyl and pyridyl. Most

20   preferably, Y is phenyl.

Preferably, m, n, p, q, r, s and t are independently 0, 1, or 2.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds

25   of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic,

30   glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, R^{1b}, R^{13}, n, p, etc.), at a particular location in a molecule, be independent of its definitions elsewhere in that molecule. Thus, $-C(R^{1a})_2$ represents $-CH_2$, $-CHCH_3$, $-CHC_2H_5$, etc. It is

5   understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

10   The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric

15   amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions

20   described in the Schemes.

<u>Synopsis of Schemes</u>

Schemes 1 to 9 describe the synthesis of compounds of formulae A and I. The starting materials can be obtained from

25   commercial sources or they can be obtained using standard transformations (e.g. esterification of the hydroxy acid) from commercially available materials.

In Scheme 1, amino-hydroxybenzoates of type II can be converted to the corresponding iodide III by treatment with acidic

30   aqueous $NaNO_2$ followed by the addition of KI. The phenol may then be alkylated by treatment with a base such as NaH or Cs_2CO_3 in an organic solvent (for example DMF) followed by the addition of an electrophile to yield IV. Reduction of the ester of IV using, for example, $LiBH_4$ in THF then yields the alcohol V which can in turn be treated with $Zn(CN)_2$ in

35   DMF and a palladium catalyst to give VI. The alcohol of VI can be

converted into a leaving group of VII in a number of ways. One such procedure involves reaction of the alcohol with a sulfonyl chloride in the presence of an organic base (e.g. triethylamine) in an organic solvent such as dichloromethane. A second method requires the reaction of the

5   alcohol with CBr_4 and a phosphine such as triphenyl phosphine in an organic solvent such as dichloromethane. A third method involves reaction of the alcohol with N-bromosuccinimide and dimethyl sulfide in dichloromethane. The reaction of VII with imidazole in a polar solvent such as DMF then affords compounds of formula IA. In addition, VII

10   upon reaction with 4-iodo-1-tritylimidazole in THF with 1,2-dibromoethane, Zn and $NiCl_2(PPh_3)_2$ and subsequent methanolysis may yield compounds of formula IB.

Scheme 2 shows an alternative route for the conversion of III into VI employing chemical transformations described above.

15   In Scheme 3, the phenol X can be converted to the corresponding triflate XI using trifluoromethane sulfonic anhydride in an organic solvent such as dichloromethane with an organic base such as triethylamine. The triflate may then be converted to the nitrile XII, the ester reduced to XIII and the alcohol transformed to a leaving group

20   as shown in XIV using previously described reactions. Treatment of XIV as above would then produce compounds of formula IC or ID.

An alternative route for the synthesis of compounds of formula IA and IB is given in Scheme 4. Methyl-hydroxybenzoic acids of structure XV may be bis alkylated by treatment with a base such as

25   NaH or Cs_2CO_3 in an organic solvent (for example DMF) followed by the addition of an electrophile to yield XVI saponification using aqueous hydroxide then affords the acid XVII. Acid XVII is then converted to the primary amide XIX via the acid chloride XVIII (prepared with thionyl chloride in a solvent such as toluene then a reaction with

30   ammonia in, for example, chloroform). Treatment of XIX with thionyl chloride in DMF results in the nitrile XX which can be brominated at the benzylic position using, for example, N-bromosuccinimide and benzoyl peroxide in carbon tetrachloride. Transformations, as before, then yield IA or IB.

An alternative route for the synthesis of compounds of formula IA and IB is shown in Scheme 5 which incorporates the reaction steps described above but alters the order of these transformations to give XXIV which is converted to IA by treatment

5   with a halide or mesylate.

Two routes to compounds containing a diaryl ether linkage as illustrated in XXVII are described in Scheme 6. The bromo fluoride XXV is transformed to the fluoro nitrile with zinc cyanide, then converted to ID in a series of transformations described in previous

10   schemes.

Scheme 7 illustrates yet another route for the synthesis of compounds of formula IA.

Schemes 8 and 9 describe routes for the preparation of compounds XXXIX and XXXX which contain a heteroatom at the

15   benzylic position between W and the phenyl ring of IA.

SCHEME 1

SCHEME 2

III → VIII

Reagents: Zn(CN)$_2$, Pd(Ph$_3$P)$_4$, DMF

VIII → Cs$_2$CO$_3$, R"Br, DMF

IX → LiBH$_4$, THF → VI
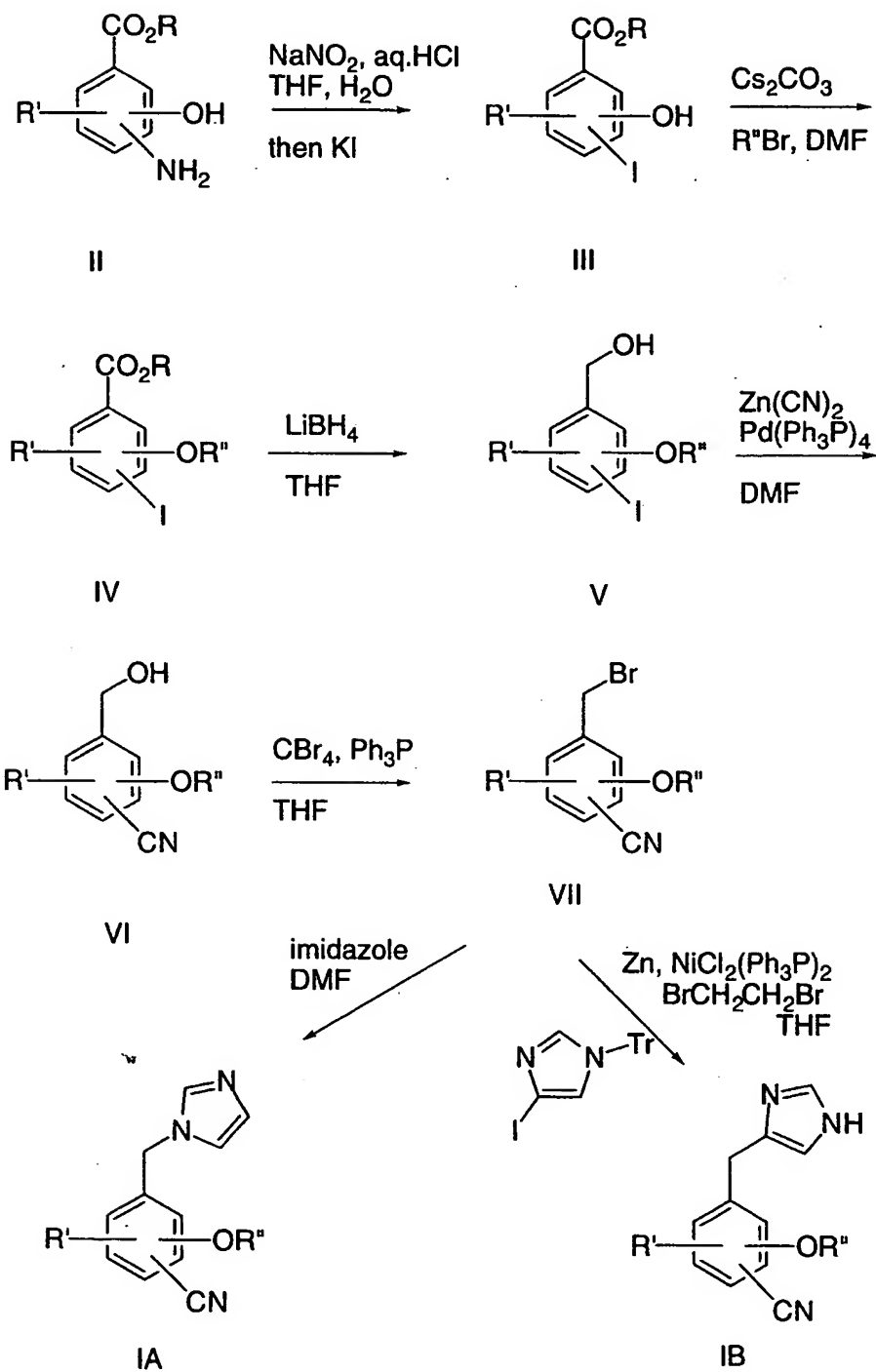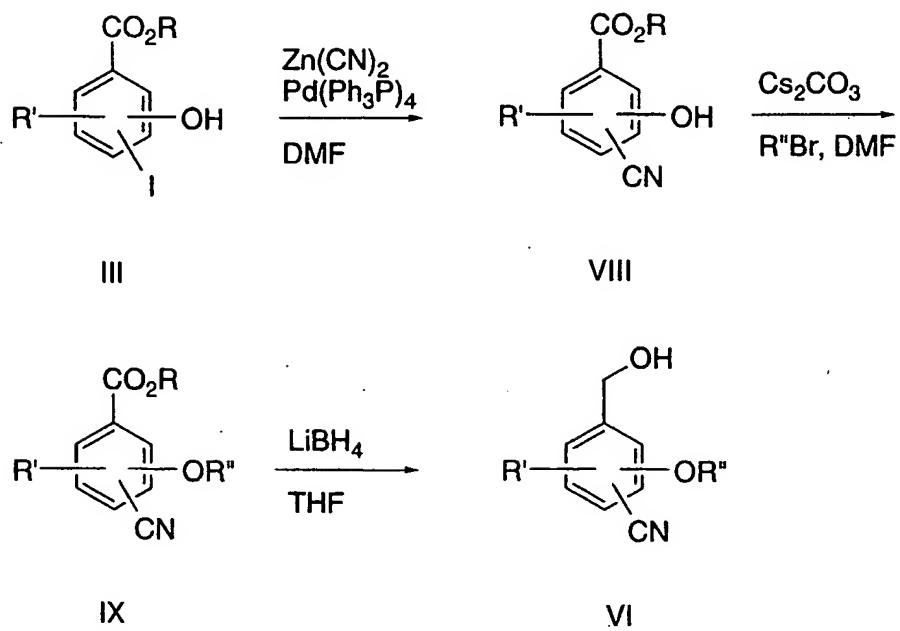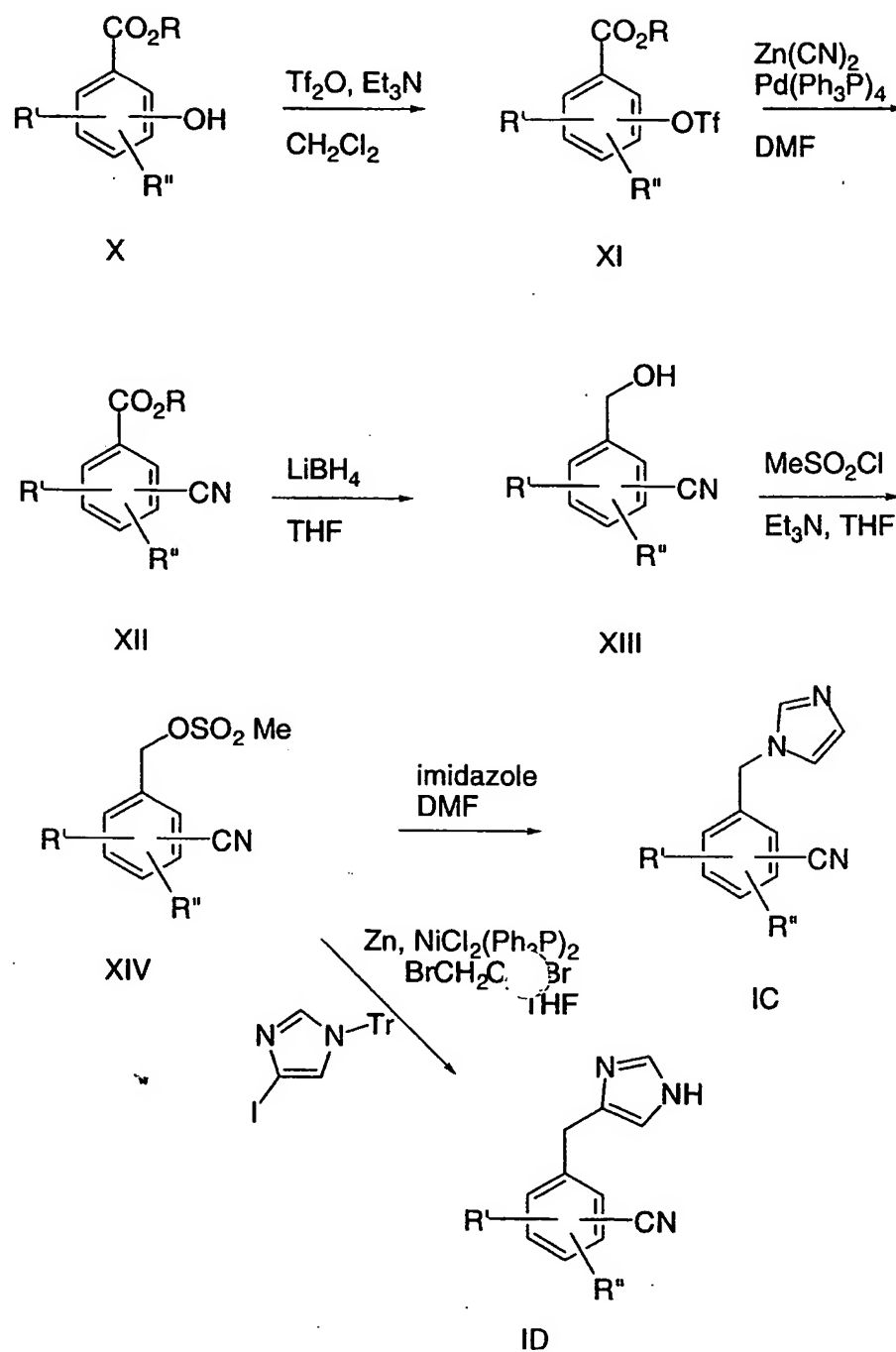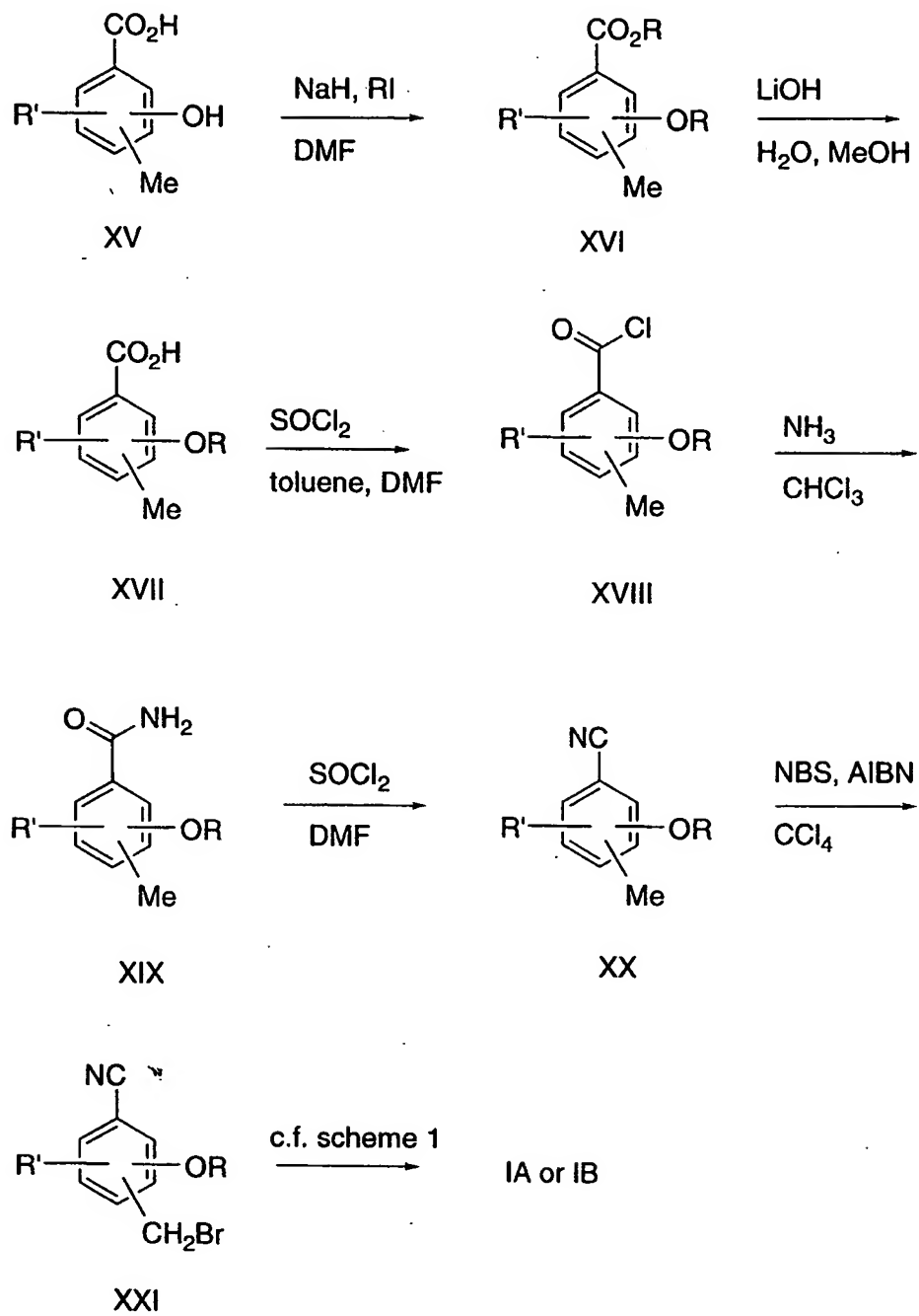
SCHEME 3

SCHEME 4

SCHEME 5
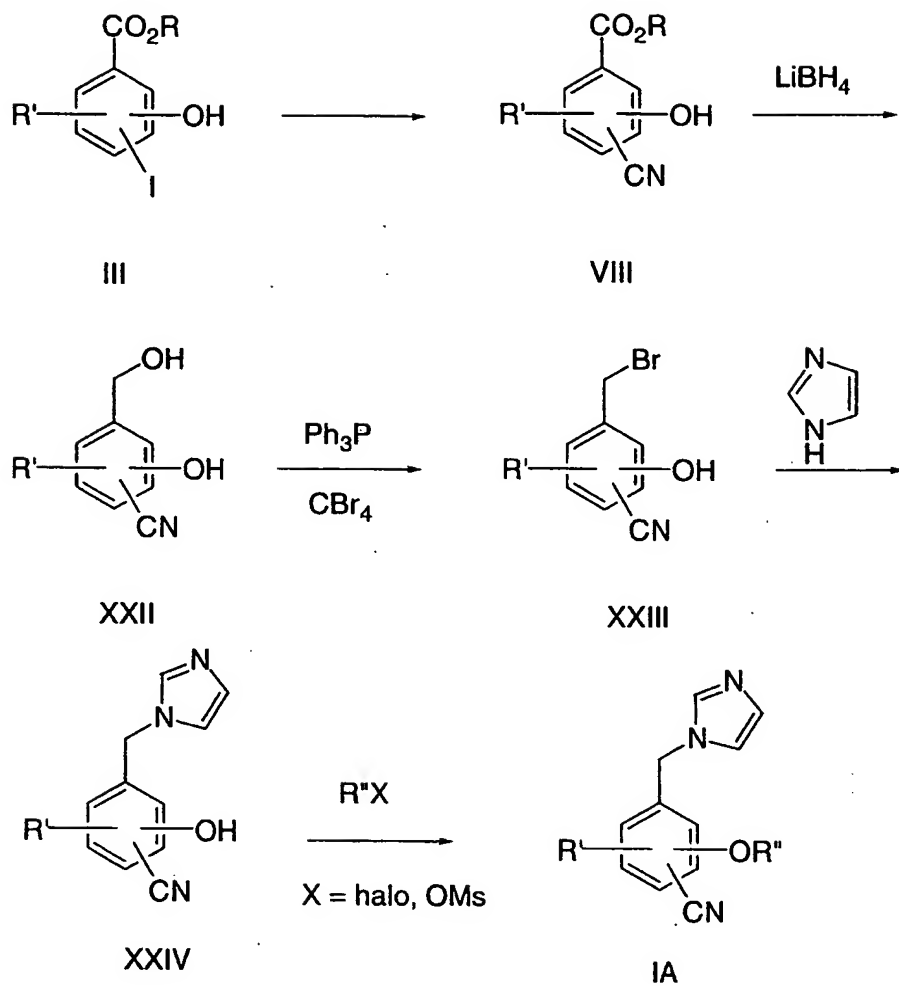
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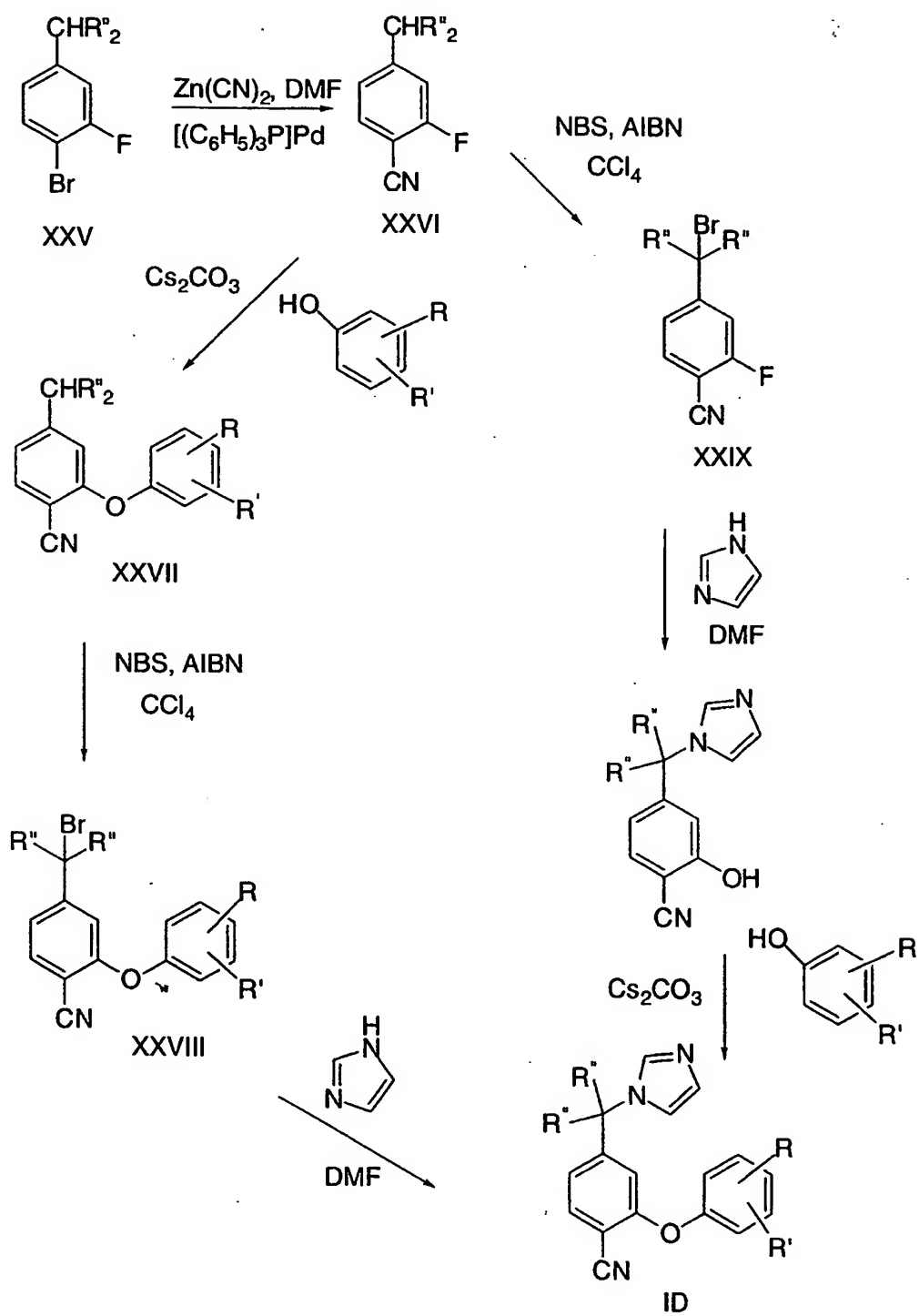
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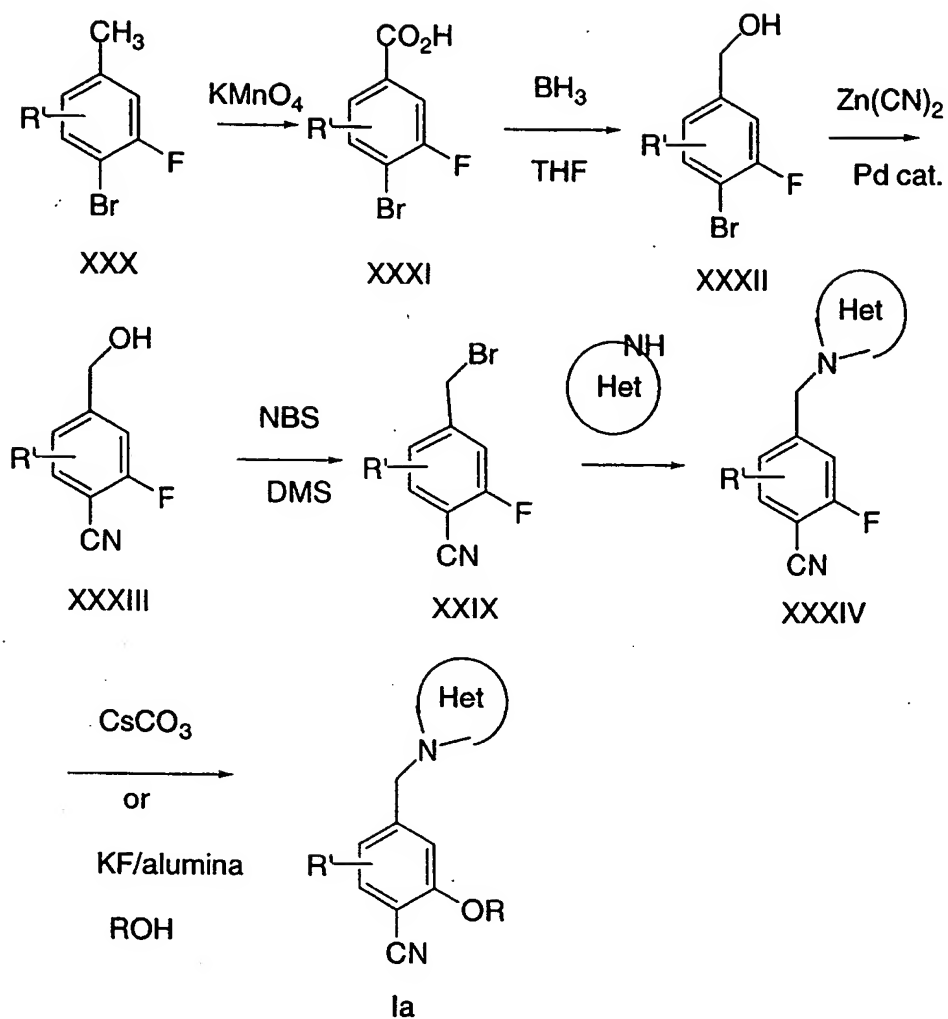
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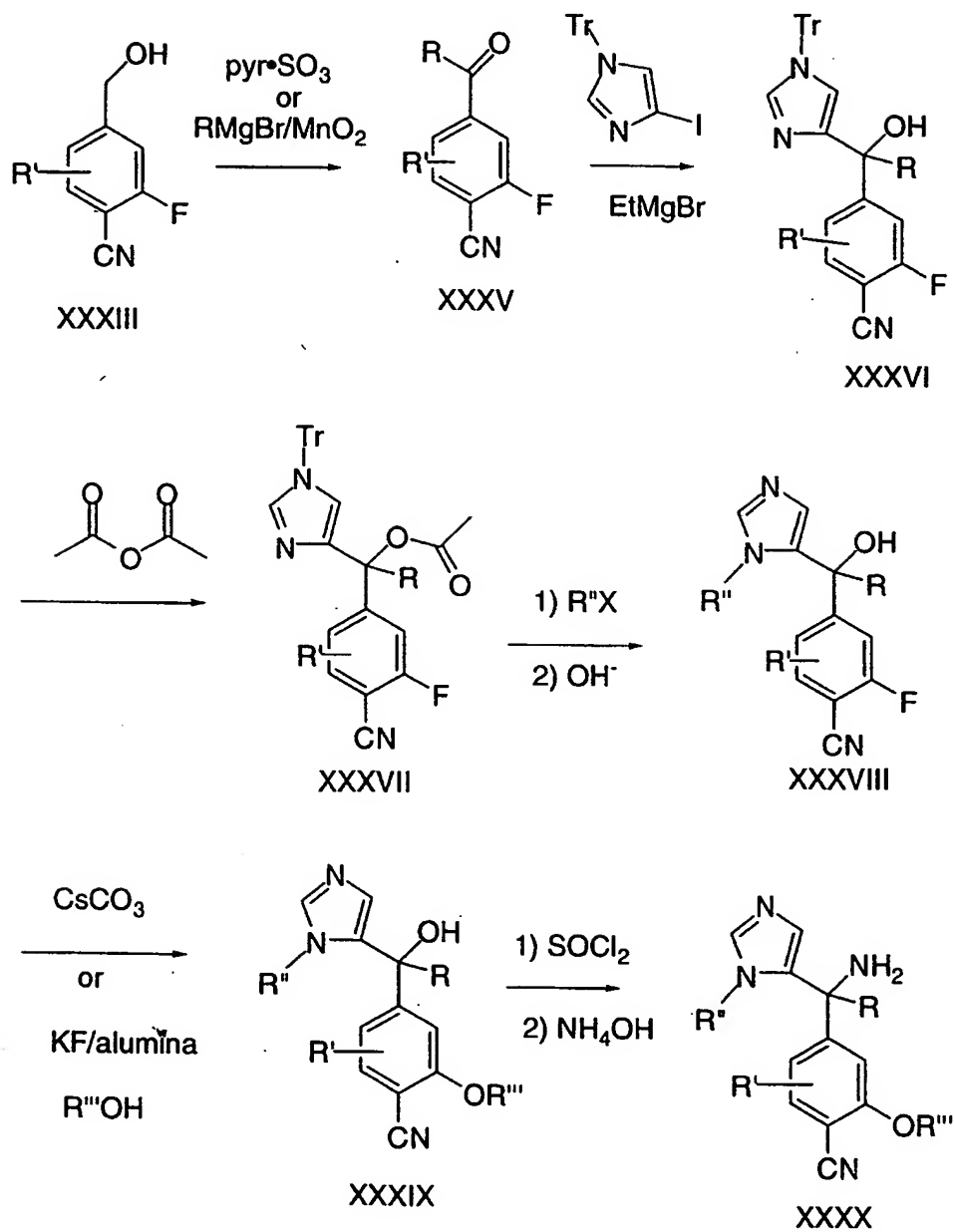
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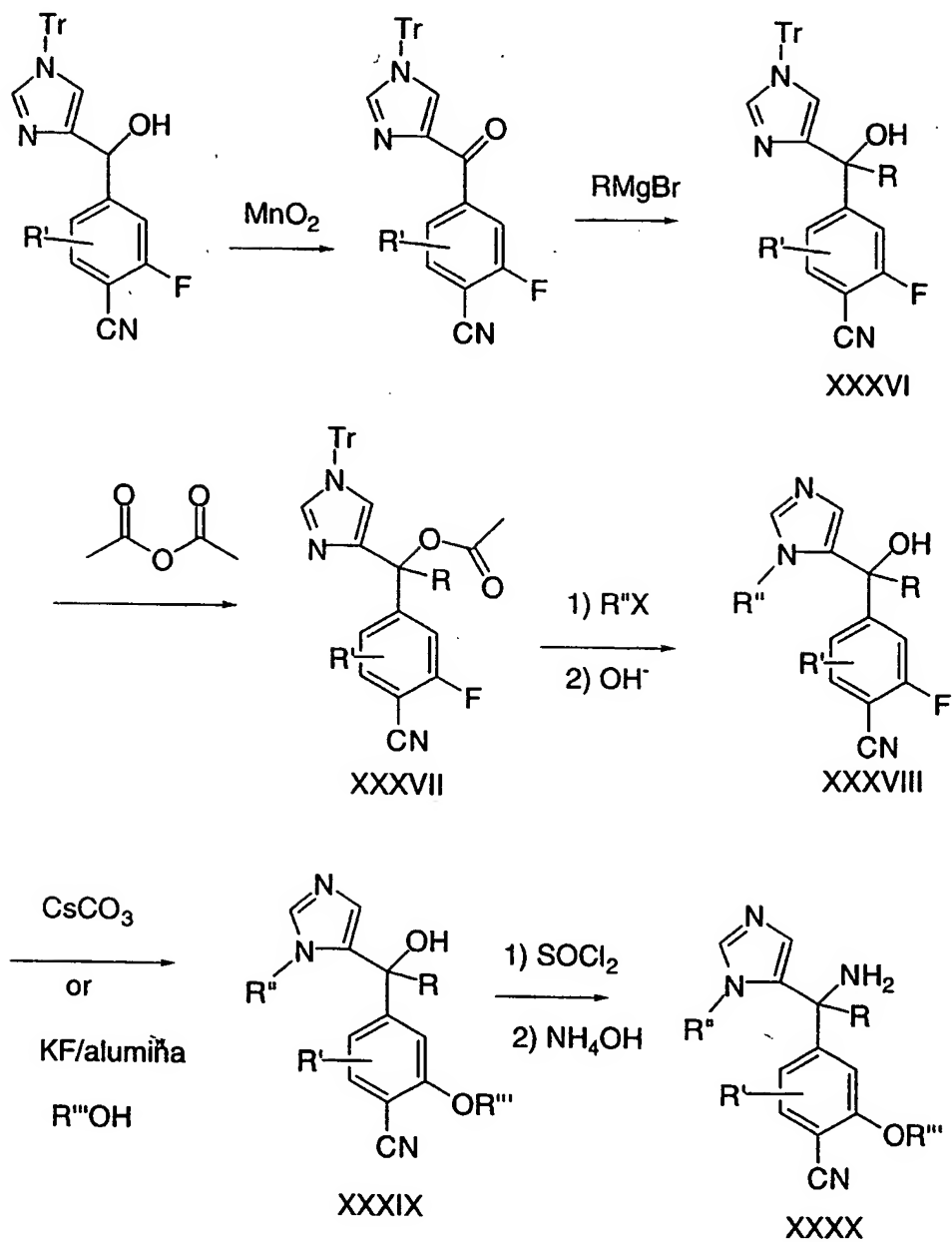
In the above Schemes, it is understood that

R independently represents R^{1c} or its protected precursors thereof;

5

R' independently represents R^3 or its protected precursors thereof;

R" independently represents R^{13} or its protected precursors

10   thereof;

R''' independently represents the following moiety:

$$(C(R^{1a})_2)_n A^2 (C(R^{1a})_2)_{\overline{n}} - X - (C(R^{1b})_2)_p A^3 (C(R^{1b})_2)_{\overline{p}} - Y \underset{R^4}{\overset{R^5}{<}}$$
$$\left(\underset{|}{R^6}\right)_t$$
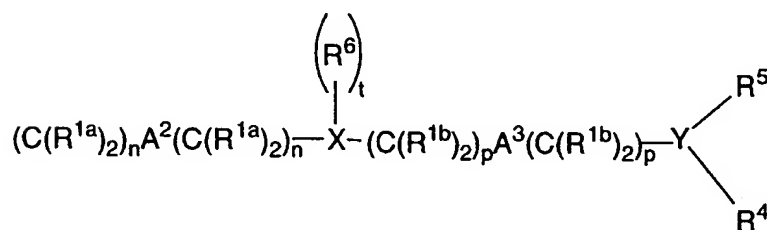
15   In a preferred embodiment of the instant invention the compounds of this instant invention are selective inhibitors of farnesyl-protein transferase. A compound is considered a selective inhibitor of farnesyl-protein transferase, for example, when its *in vitro* farnesyl-protein transferase inhibitory activity, as assessed by the assay described

20   in Example 29, is at least 100 times greater than the *in vitro* activity of the same compound against geranylgeranyl-protein transferase-type I in the assay described in Example 30. Preferably, a selective compound exhibits at least 1000 times greater activity against one of the enzymatic activities when comparing geranylgeranyl-protein transferase-type I

25   inhibition and farnesyl-protein transferase inhibition.

          In another preferred embodiment of the instant invention the compounds of this instant invention are dual inhibitors of farnesyl-protein transferase and geranylgeranyl-protein transferase type I. Such

a dual inhibitor will exhibit certain characteristics when assessed in *in vitro* assays, which are dependent on the type of assay employed.

In a SEAP assay, such as described in Example 33, it is preferred that the dual inhibitor compound has an *in vitro* inhibitory

5   activity (IC_{50}) that is less than about 12μM against K4B-Ras dependent activation of MAP kinases in cells. More preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) against K4B-Ras dependent activation of MAP kinases in cells which is more than about 5 times lower than the inhibitory activity (IC_{50}) against Myr-Ras

10   dependent activation of MAP kinases in cells. Also more preferably, in a SEAP assay, the dual inhibitor compound has an inhibitory activity (IC_{50}) that is less than about 10 nM against H-Ras dependent activation of MAP kinases in cells.

In a GGTase plus anion assay, such as described in

15   Example 30, it is preferred that the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion. More preferably, the dual

20   inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 1 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion. Preferably, the dual inhibitor compound has an *in*

25   *vitro* inhibitory activity (IC_{50}) in the in vitro assay as described in Example 29 that is less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate, comprising a $CAAX^F$ motif, by farnesyl-protein transferase. More preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than

30   about 100nM against transfer of a farnesyl residue to a protein or peptide substrate, comprising a $CAAX^F$ motif, by farnesyl-protein transferase. Also preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) in the in vitro assay as described in Example 32, that is less than about 100 nM against the anchorage independent growth of

35   H-*ras*-transformed mammalian fibroblasts.

-70-

The protein or peptide substrate utilized in the instant assay may incorporate any CAAX motif that is geranylgeranylated by GGTase-I. The term "CAAX^G" will refer to such motifs that may be geranylgeranylated by GGTase-I. It is understood that some of the

5 "CAAX^G" containing protein or peptide substrates may also be farnesylated by farnesyl-protein transferase. In particular such "CAAX^G" motifs include (the corresponding human protein is in parentheses): CVIM (K4B-Ras) (SEQ.ID.NO.: 1), CVLL (mutated H-Ras) (SEQ.ID.NO.: 2), CVVM (N-Ras) (SEQ.ID.NO.: 3), CIIM (K4A-Ras)

10 (SEQ.ID.NO.: 4), CLLL (Rap-IA) (SEQ.ID.NO.: 5), CQLL (Rap-IB) (SEQ.ID.NO.: 6), CSIM (SEQ.ID.NO.: 7), CAIM (SEQ.ID.NO.: 8), CKVL (SEQ.ID.NO.: 9), and CLIM (PFX) (SEQ.ID.NO.: 10). Preferably, the CAAX motif is CVIM.

As used herein, the term "CAAX^F" is used to designate a

15 protein or peptide substrate that incorporates four amino acid C-terminus motif that is farnesylated by farnesyl-protein transferase. It is understood that certain of the "CAAX^F" containing protein or peptide substrates may also be geranylgeranylated by GGTase-I. In particular such "CAAX^F" motifs include (the corresponding human protein is in

20 parentheses): CVLS (H-ras) (SEQ.ID.NO.: 11), CVIM (K4B-Ras) and CVVM (N-Ras).

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples

25 of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e.,

30 neurofibromin (NF-1), neu, src, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit a prenyl-protein transferase and, in particular, the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor

angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55: 4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of vision deficit related to retinal vascularization.

5   The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished
10   by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis
15   delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

20   The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the
25   treatment of fungal infections.

The instant compounds may also be useful as inhibitors of proliferation of vascular smooth muscle cells and therefore useful in the prevention and therapy of arteriosclerosis and diabetic vascular pathologies.

30   The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or
35   parenterally, including the intravenous, intramuscular,

intraperitoneal, subcutaneous, rectal and topical routes of administration.

5

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents

10

selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

15

These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate,

20

stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

25

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or

30

olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-

35

cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and

- 73 -

gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic

5   alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan

10   monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the

15   active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral

20   preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending

25   agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also

30   be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol

35   anhydrides, for example sorbitan monooleate, and condensation

products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening
5   agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension
10   may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among
15   the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such
20   as oleic acid find use in the preparation of injectables.

The injectable suspensions or solutions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the suspensions or solution in such a way as to maintain a constant circulating concentration of the instant
25   compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

Compounds of Formula A may also be administered in the
30   form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

5   The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage

10   administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of

15   polyethylene glycol.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or

20   indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally

25   varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg

30   of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are

35   selected for their particular usefulness against the condition that is

being treated. For example, the compounds of the instant invention may also be co-administered with other well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such
5   combinations of therapeutic agents are combinations of the instant prenyl-protein transferase inhibitors and an antineoplastic agent. It is also understood that such a combination of antineoplastic agent and inhibitor of a prenyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors,
10   including radiation therapy and surgery.

Examples of an antineoplastic agent include, in general, microtubule-stabilizing agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives);
15   microtubule-disruptor agents; alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.
20   Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes
25   include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide,
30   melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase,

camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

The preferred class of antineoplastic agents is the taxanes and the preferred antineoplastic agent is paclitaxel.

5   Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with the instant inhibitor of a prenyl-protein transferase alone to treat cancer.

Additionally, compounds of the instant invention may also

10   be useful as radiation sensitizers, as described in WO 97/38697, published on October 23, 1997, and herein incorporated by reference.

The instant compounds may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular

15   proliferation. Thus, the instant compounds may be utilized in combination with farnesyl pyrophosphate competitive inhibitors of the activity of farnesyl-protein transferase or in combination with a compound which has Raf antagonist activity. The instant compounds may also be co-administered with compounds that are selective

20   inhibitors of geranylgeranyl protein transferase. In particular, if the compound of the instant invention is a selective inhibitor of farnesyl-protein transferase, co-administered with a compound(s) that is a selective inhibitor of geranylgeranyl protein transferase may provide the therapeutic effect of administration of a dual inhibitor as described

25   hereinabove, and thus offer certain advantages over administration of only the compound of the instant invention.

In particular, the compounds disclosed in the following patents and publications may be useful as farnesyl pyrophosphate-competitive inhibitor component of the instant composition: U.S. Ser.

30   Nos. 08/254,228 and 08/435,047. Those patents and publications are incorporated herein by reference.

In practicing methods of this invention, which comprise administering, simultaneously or sequentially or in any order, two or more of a protein substrate-competitive inhibitor and a farnesyl

35   pyrophosphate-competitive inhibitor, such administration can be orally

or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration. It is preferred that such administration be orally. It is more preferred that such administration be orally and simultaneously. When the protein

5   substrate-competitive inhibitor and farnesyl pyrophosphate-competitive inhibitor are administered sequentially, the administration of each can be by the same method or by different methods.

The instant compounds may also be useful in combination with an integrin antagonist for the treatment of cancer, as described in

10 U.S. Ser. No. 09/055,487, filed April 6, 1998, which is incorporated herein by reference.

As used herein the term an integrin antagonist refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to an integrin(s) that is involved in the

15 regulation of angiogenisis, or in the growth and invasiveness of tumor cells. In particular, the term refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 3$ integrin, which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, which antagonize,

20 inhibit or counteract binding of a physiological ligand to both the $\alpha v\beta 3$ integrin and the $\alpha v\beta 5$ integrin, or which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins. The term also refers to

25 antagonists of any combination of $\alpha v\beta 3$ integrin, $\alpha v\beta 5$ integrin, $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins. The instant compounds may also be useful with other agents that inhibit angiogenisis and thereby inhibit the growth and invasiveness of tumor cells, including, but not limited to angiostatin and endostatin.

30 Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restenosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the combinations of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Combinations of the instant invention may

5   alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

For oral use of a chemotherapeutic compound according to
10   this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral
15   administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and
20   intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-
25   administered with other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that
30   are effective in the treatment and prevention of NF-1, restinosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range
35   described below and the other pharmaceutically active agent(s) within

its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical

5   composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacolo-

10   gically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and

15   quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a

20   compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques.

25   Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence

30   of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the

35   instant invention may be used in an active site titration assay to

determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine

5   terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the

10   enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

15   Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

20   ## EXAMPLE 1

Preparation of 3-(biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-
benzonitrile

25   Step A: Preparation of phenyl 2-hydroxy-4-iodobenzoate
                   A solution of NaNO$_2$ (1.33 g, 19.3 mmol) in 10 mL water was
       added to a solution of phenyl-4-amino-2-hydroxybenzoate (4.02 g, 17.6
       mmol) in 3N HCl (35 mL) and THF (10 mL) at 0°C. The resulting yellow
       solution was stirred for 30 minutes then KI (8.74 g, 52.7 mmol) in water

30   (13 mL) was added. After 10 minutes, the dark brown/red slurry was
       poured into EtOAc, washed twice with water then with aqueous sodium
       bisulfite and brine. The dried (MgSO$_4$) solution was filtered and
       concentrated to give a dark oil. Column chromatography (silica gel;
       hexane:EtOAc 15:1) gave the title compound as a white solid which

contained approximately 15% of an unidentified impurity. This material was used as such in the next step.

Step B: Preparation of phenyl 4-iodo-2-(biphenyl-4-ylmethoxy) benzoate

To a solution of a phenol, as described in Step A, in 10 mL of dimethyl formamide (DMF) was added 4-phenylbenzyliodide (292 mg, 0.99 mmol) and Cs_2CO_3 (442 mg, 1.35 mmol) and the suspension was stirred for 16 hr. After this time, the reaction mixture was diluted with EtOAc, extracted with water (3X), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; hexane:EtOAc 20:1) to provide an oil which crystallized from ether:hexane 1:10 to give the title compound as a white solid.

^{1}H NMR (CDCl$_3$) d 5.23 (2H, s), 7.17 (2H, m), 7.25 (1H, m), 7.3-7.6 (13H, m), 7.75 (1H, d).

Step C: Preparation of 4-iodo-2-(biphenyl-4-ylmethoxy) benzylalcohol

To a solution of an ester, as described in Step B, in 5 mL of THF was added lithium borohydride (28 mg, 1.27 mmol) and heated at reflux for 30 minutes. After this time, the reaction mixture was poured into EtOAc and extracted with 1N HCl, then water, and then brine. The organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound as a white solid :

^{1}H NMR(CDCl$_3$) d 2.17 (1H, t), 4.70 (2H, d), 5.12 (2H, s), 7.07 (1H, d), 7.3-7.7 (11H, m).

Step D: Preparation of 4-cyano-2-(biphenyl-4-ylmethoxy) benzylalcohol

A solution of an iodide, as described in Step C, and $Zn(CN)_2$ (49 mg, 0.42 mmol) in DMF (5 mL) was degassed with argon for 15 minutes. Pd(Ph$_3$P)$_4$ (35 mg, 0.03 mmol) was added and the mixture heated to 80°C for 16 hr. The mixture was poured into water and extracted with EtOAc (2X). The organic layers were washed with 1N HCl, water and then brine. They were then dried ($MgSO_4$) and the

solvent removed. Chromatography of the residue (silica gel; hexane:EtOAc 2:1) afforded the title compound as a white solid.

^{1}H NMR(CDCl$_3$) d 2.18 (1H, t), 4.81 (2H, d), 5.17 (2H, s), 7.19 (1H, d), 7.3-7.65(11H, m)

5

Step E: Preparation of methanesulfonic acid 2-(biphenyl-4-ylmethoxy)-4-cyanobenzyl ester

A solution of an alcohol, as described in Step D, in dichloromethane (4 mL) at room temperature, was treated sequentially
10   with Et$_3$N (81 µL, 0.59 mmol) and methanesulfonyl chloride (32 µL, 0.41 mmol). After 1 hr, a further Et$_3$N (81 µL, 0.59 mmol) and methanesulfonyl chloride (32 µL, 0.41 mmol) was added and stirred for another hour. The solution was poured into water, extracted with EtOAc, washed with brine, dried (MgSO$_4$) and evaporated to give a solid.
15   Column chromatography (silica gel; hexane:EtOAc 2:1) gave the title compound as a solid. Rf (silica): 0.37 (hexane:EtOAc 2:1).

^{1}H NMR(CDCl$_3$) d 2.95 (3H, s), 5.18 (2H, s), 5.35 (2H, s), 7.2-7.7 (12H, m).

Step F: Preparation of 3-(biphenyl-4-ylmethoxy)-4-imidazol-1-
20   ylmethyl-benzonitrile

A solution of a mesylate, as described in Step E and imidazole (45 mg, 0.66 mmol) in DMF (1.5 mL) was stirred at room temperature for 16 hr. The mixture was poured into a saturate NaHCO$_3$ solution, extracted with EtOAc, washed with water and then brine,
25   dried (MgSO$_4$) and evaporated to give a solid. Column chromatography (silica gel; 2% MeOH in CHCl$_3$) gave an oil which crystallized from ether to afford the title compound.

^{1}H NMR(CDCl$_3$) d 5.16 (2H, s), 5.20 (2H, s), 6.89 (1H, t), 7.00 (1H, d), 7.09 (1H, s), 7.24 (2H, m), 7.35-7.5 (5H, m), 7.53 (1H, s), 7.6-7.68 (4H, m).
30   Analysis calculated for C$_{24}$H$_{19}$N$_3$O:

C, 78.88; H, 5.24; N, 11.50;

Found: C, 78.67; H, 5.54; N, 11.31.

35

EXAMPLE 2

Preparation of 3-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-
ylmethylbenzonitrile hydrochloride

5

Step A: Preparation of phenyl 4-cyano-2-hydroxybenzoate

A solution of phenyl 2-hydroxy-4-iodobenzoate, as described
in Example 1, Step A, (2.38 g, 7.0 mmol) and Zn(CN)$_2$ (575 mg, 4.9 mmol)
in DMF was degassed with argon for 25 minutes. Pd(Ph3P)$_4$ (404 mg,

10   0.35 mmol) was added and the mixture heated to 80°C for 16 hr. The
mixture was poured into 1N HCl and extracted with EtOAc (2X), washed
with water then brine, dried (MgSO$_4$) and the solvent removed.
Chromatography of the residue (silica gel; hexane:EtOAc 9:1) afforded
the title compound as a white solid.

15   ^{1}H NMR(CDCl3) d 7.18-7.28 (3H, m), 7.35 (2H, m), 7.48 (2H, m), 8.19 (1H,
d), 10.67 (1H, s).

Step B: Preparation of phenyl 4-cyano-2-(biphenyl-4-yl-2-ethoxy)
benzoate

20   To a solution of a phenol, as described in Step A, in 5 mL of
dimethyl formamide (DMF) was added biphenyl-4-ylethyl iodide (170 mg,
0.55 mmol) and Cs2CO3 (246 mg, 0.75 mmol). The suspension was
stirred for 16 hr. After this time, the reaction mixture was diluted with
EtOAc, extracted with water (3X), washed with brine, dried (MgSO$_4$)

25   and concentrated in vacuo. The residue was purified by flash
chromatography (SiO2; hexane:EtOAc 9:1 then 4:1) to provide the title
compound.
Rf (silica): 0.22 (hexane:EtOAc 9:1).

30   Step C: Preparation of 4-cyano-2-(biphenyl-4-yl-2-ethoxy) benzyl
alcohol

To a solution of an ester, as described in Step B, in 3 mL of
THF was added lithium borohydride (9.6 mg, 0.44 mmol) and heated at
reflux for 1 hr. After this time, the reaction mixture was poured into

35   EtOAc and extracted with 1N HCl, then water, then brine. The organic

layer was separated, dried (MgSO$_4$) and evaporated *in vacuo* to afford the title compound as an oil. The residue was purified by flash chromatography (SiO$_2$; hexane:EtOAc 2:1) to provide the title compound.

^{1}H NMR(CDCl$_3$) d 2.16 (1H, t), 3.17 (2H, t), 4.25 (2H, t), 4.65 (1H, d), 7.06 (1H, d), 7.24 (1H, dd), 7.3-7.45 (6H, m), 7.55-7.6 (4H, m).

Step D: Preparation of 3-(biphenyl-4-yl-2-ethoxy)-4-bromomethyl-
             benzonitrile

A mixture of an alcohol, as described in Step C, carbon tetrabromide (68 mg, 0.205 mmol) and PPh$_3$ (54 mg, 0.205 mmol) in THF (2 mL) was stirred for 16 hr. More carbon tetrabromide (68 mg, 0.205 mmol) and PPh$_3$ (54 mg, 0.205 mmol) were added and stirring continued for 24 hr. The solution was diluted with ether, filtered and the solvent concentrated. Chromatography of the residue (silica gel; hexane:EtOAc 9:1) afforded the title compound.

Rf (silica): 0.78 (hexane:EtOAc 2:1).

Step E: Preparation of 3-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-
             ylmethyl-benzonitrile hydrochloride

A solution of a bromide, as described in Step D, and imidazole (26 mg, 0.38 mmol) in DMF (2 mL) was stirred at room temperature for 16 hr. The mixture was poured into saturate NaHCO$_3$ solution, extracted with EtOAc, washed with water then brine, dried (MgSO$_4$) and evaporated to give a solid. Column chromatography (silica gel; hexane:EtOAc 1:1 then 2% MeOH in CHCl$_3$) gave an oil which was treated with 0.5 mL 1N HCl in ether to afford (after removal of the ether) the title compound as a solid.

^{1}H NMR(CD$_3$OD) d 3.18 (2H, t), 4.44 (2H, t), 5.38 (2H, s), 7.2-7.5 (10H, m), 7.5-7.7 (4H, m), 8.62 (1H, s).

EXAMPLE 3

Preparation of 3-(biphenyl-3-ylmethoxy)-4-imidazol-1-ylmethyl-
benzonitrile hydrochloride

5   Following the procedure described in Example 2, Steps A to
F, but using biphenyl-3-ylmethyl bromide, as described in Step B, as
starting material, the title compound was obtained as a solid.
^{1}H NMR(CD$_3$OD) d 5.27 (2H, s), 5.52 (2H, s), 7.3-7.7 (14H, m), 8.85 (1H, s).

10   EXAMPLE 4

Preparation of 2-(biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-
benzonitrile

15   Step A: Preparation of methyl 4-amino-3-hydroxybenzoate
             HCl (g) was bubbled through a solution of 4-amino-3-
hydroxybenzoic acid (7 g, 54.8 mmol) in MeOH (450 mL) until saturated
then the mixture was heated at 70°C for 16 hr. The mixture was
concentrated in vacuo, the residue taken up in EtOAc, washed with
20   saturated NaHCO$_3$ then brine and dried (MgSO$_4$). Removal of the
solvent yielded the title compound as a brown solid.
^{1}H NMR(CD$_3$OD) d 3.80 (3H, s), 6.66 (1H, d), 7.32 (1H, dd), 7.37 (1H, dd).

     Step B: Preparation of methyl 3-hydroxy-4-iodobenzoate
25   A solution of NaNO$_2$ (15.89 g, 0.092 mol) in water (30 mL)
was added to a solution of methyl 4-amino-3-hydroxybenzoate (14.00 g,
0.084 mol) in 3N HCl (120 mL) and THF (20 mL) at 0°C. The resulting
dark red solution was stirred for 30 minutes then KI (41.68 g, 2.51 mol)
in water (30 mL) was added. After 10 minutes, the dark brown/red
30   slurry was poured into EtOAc, washed twice with water then with
aqueous sodium bisulfite and brine. The dried (MgSO$_4$) solution was
filtered and concentrated to give a dark oil. Column chromatography
(silica gel; hexane:EtOAc 15:1) gave the title compound.

Step C: Preparation of methyl 4-cyano-3-hydroxybenzoate

A solution of methyl 3-hydroxy-4-iodobenzoate (2.38 g, 7.0 mmol) (as described in Step B) and Zn(CN)2 (0.575 g, 4.9 mmol) in DMF was degassed with argon for 25 minutes. Pd(Ph3P)4 (0.404 g, 0.35

5   mmol) was added and the mixture heated to 80°C for 16 hr. The mixture was poured into 1N HCl and extracted with EtOAc (2X), washed with water then brine, dried (MgSO4) and the solvent removed. Chromatography of the residue (silica gel; hexane:EtOAc 9:1) afforded the title compound as a white solid.

10   ^{1}H NMR(CDCl3) d 3.95 (3H, s), 6.54 (1H, br s), 7.60 (1H, d), 7.65 (1H, d), 7.570 (1H, s).

Step D: Preparation of 2-Hydroxy-4-hydroxymethylbenzonitrile

Methyl 4-cyano-3-hydroxybenzoate (as described in Example

15   4, Step C) (0.50 g, 2.82 mmol) was dissolved in dry THF (30 mL), treated with LiBH$_4$ (2.0M solution in THF) (5.64 mL, 11.28 mmol) and heated at reflux overnight. The reaction mixture was concentrated, then partitioned between EtOAc (50 mL) and 1N HCl (50 mL), the aqueous layer extracted with additional EtOAc (2 x 50 mL), the organic layers

20   combined, washed with brine, and dried (MgSO$_4$). Filtration and concentration to dryness gave the title compound.
^{1}H NMR (CD$_3$OD) δ 7.45 (1H, d, J = 8 Hz), 6.98 (1H, d, J = 1 Hz), 6.89 (1H, dd, J = 1, 8, Hz), 4.58 (2H, s).

25   Step E: Preparation of 4-Bromomethyl-2-hydroxy-benzonitrile

2-Hydroxy-4-hydroxymethylbenzonitrile (0.20 g, 1.34 mmol) was dissolved in DMF (5 mL) - CH$_2$Cl$_2$(5 mL) and treated with triphenylphosphine (0.53 g, 2.01 mmol) and carbon tetrabromide (0.67 g, 2.01 mmol) at ambient temperature with stirring. After 2 h the reaction

30   mixture was partitioned between EtOAc (100 mL) - H$_2$O (100 mL), the organic layer separated, dried (MgSO$_4$), and filtered to give the title compound after silica gel chromatography (15% EtOAc/ hexane to 25%EtOAc/ hexane).
^{1}H NMR (CD$_3$OD) δ 7.45 (1H, d, J = 8 Hz), 6.94 (1H, s), 6.90 (1H, d, J =8,

35   Hz), 4.40 (2H, s).

<u>Step F:</u>   Preparation of 2-Hydroxy-4-imidazol-1-ylmethyl-
              benzonitrile

          4-Bromomethyl-2-hydroxy-benzonitrile (0.22 g, 1.05 mmol)
5   and imidazole (0.36 g, 5.23 mmol) were dissolved in DMF (10 mL) with
     stirring at ambient temperature. After stirring for 18 h the reaction
     mixture was concentrated *in vacuo* and purified by silica gel
     chromatography eluting with 2% $CH_3OH/\ CH_2Cl_2$ to 5% $CH_3OH/\ CH_2Cl_2$
     to give the title compound.
10   ^{1}H NMR (DMSO) δ 11.11 (1H, s), 7.74 (1H, s), 7.58 (1H, d, J = 8 Hz), 7.17
     (1H, s), 6.95 (1H, s), 6.74 (1H, d, J =8, Hz), 6.69 (1H, s), 5.23 (2H, s).

<u>Step G:</u>   Preparation of 2-(biphenyl-4-ylmethoxy)-4-imidazol-1-
              ylmethyl-benzonitrile

15   Following the procedure described in Example 2, Step E but
     using 2-hydroxy-4-imidazol-1-ylmethyl-benzonitrile (as described in Step
     F) and biphenyl-4-ylmethyl iodide as starting materials, the title
     compound was obtained as a solid.
     ^{1}H NMR(CD3OD) d 4.89 (2H, s), 5.28 (2H, s), 6.91 (1H, d), 7.06 (3H, m),
20   7.3-7.55 (5H, m), 7.6-7.66 (5H, m), 7.77 (1H, s).
     Analysis calculated for $C_{24}H_{19}N_3O$:

              C, 78.88; H, 5.24; N, 11.50;
     Found: C, 78.59; H, 5.31; N, 11.10.

25   <u>EXAMPLE 5</u>

     Preparation of 2-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-ylmethyl-
     benzonitrile hydrochloride

              Following the procedure described in Example 4, Step A to
30   D but using biphenyl-4-ylethyl iodide as the starting material in Step B,
     and treatment of the final product with 1N HCl in ether, the title
     compound was obtained as a solid.
     ^{1}H NMR(CD3OD) d 3.13 (2H, t), 4.28 (2H, t), 4.90 (2H, s), 6.83 (1H, dd),
     6.95 (1H, s), 7.00 (1H, t), 7.11 (1H, t), 7.30 (1H, m), 7.35-7.45 (4H, m), 7.5-
35   7.6 (5H, m), 7.76 (1H, s).

EXAMPLE 6

Preparation of 1-*tert*-butoxycarbonyl-4-(3-chlorophenyl)-2(S)-[2-(2-cyano-
5   5-imidazol-1-ylmethyl-phenoxy)ethyl]piperazine

Step A: Preparation of L-N-*tert*-butoxycarbonyl homoserine lactone
              To a solution of L-homoserine lactone hydrochloride (10 g,
72.7 mmol) and (Boc)2O (19.0 g, 87.2 mmol) in dichloromethane (200 mL)
10   at 0°C was added Et3N (12.2 mL, 87.2 mmol) dropwise. The solution was
warmed to room temperature and stirred for 16 hr. The mixture was
poured into 10% citric acid solution, extracted with EtOAc, washed with
saturated NaHCO3 solution, then brine, dried (MgSO4) and evaporated
in vacuo. Column chromatography (silica gel; hexane:EtOAc 1:1 then
15   pure EtOAc) afforded the title compound as a white solid.
Rf (silica): 0.58 (hexane:EtOAc 1:1).

Step B: Preparation of L-N-*tert*-butoxycarbonyl homoserine lactol
              To a solution of a lactone, as described in Step A, in THF
20   (355 mL) at -78°C was added DIBAL-H (1.0M in THF; 146 mL, 146 mmol)
dropwise. The solution was stirred at -78°C for 1 hr then EtOAc and
sodium potassium tartrate solution were added and the resulting
mixture stirred vigorously for 30 minutes. After extracting with EtOAc
(4X) the combined organic layers were washed with brine and dried over
25   MgSO4. Removal of the solvent yielded an oil which solidified on
standing. Column chromatography (silica gel; hexane:EtOAc 2:1 then
1:1) afforded the title compound as a white solid.

Step C: Preparation of 3(S)-(N'-*tert*-butoxycarbonylamino)-4-(N
30   3-chlorophenylamino)-butanol
              To a solution of a lactol, as described in Step B, and 3-
chloroaniline (6.25 mL, 59.1 mmol) in dichloroethane (200 mL) at room
temperature was added acetic acid (3.07 mL, 53.7 mmol) followed by
Na(OAc)3BH (17.1 g, 80.5 mmol) and the mixture stirred for 2 hr.
35   Saturated NaHCO3 solution was added and the mixture extracted with

dichloromethane (3X), washed with brine, dried (MgSO4) and concentrated *in vacuo*. Column chromatography (silica gel; hexane:EtOAc 2:1 then 1:1 then pure EtOAc) afforded the title compound as a white solid.

5   ^{1}H NMR(CDCl3) d 1.45 (9H, s), 1.5 (1H, m), 1.90 (1H, m), 2.96 (1H, br s), 3.11 (1H, m), 3.24 (1H, m), 3.73 (2H, m), 4.05 (2H, m), 4.75 (1H, d), 6.48 (1H, dd), 6.58 (1H, t), 6.67 (1H, dd), 7.07 (1H, t).

Step D: Preparation of 3(S)-(N'-*tert*-butoxycarbonylamino)-4-(N-3-
10   chlorophenyl-N-chloroacetyl)amino-butanol

        To a solution of an amine, as described in Step C, in EtOAc (120 mL) and saturated NaHCO3 (120 mL) at 0°C was added chloroacetyl chloride (3.08 mL, 38.8 mL) dropwise. After 2 hr, the mixture was extracted with EtOAc (3X), washed with brine, dried (MgSO4) and
15   concentrated *in vacuo* to give the title product as a clear oil which was used as such.

Step E: Preparation of 1-*tert*-butoxycarbonyl-4-(3-chlorophenyl)-
              2(S)-(2-hydroxyethyl)-5-oxo-piperazine
20   To a solution of a chloroacetamide, as described in Step D, in DMF (100 mL) at 0°C was added Cs2CO3 (27.75 g, 85.2 mmol) and the reaction was stirred for 6 hr. The solution was poured into EtOAc and saturated NH4Cl. Extracted with EtOAc (3X), washed with brine, dried and evaporated to give a yellow oil. Column chromatography (silica gel;
25   hexane:EtOAc 2:1 then 1:1 then pure EtOAc) afforded the title compound as a clear oil.

Step F: Preparation of 1-*tert*-butoxycarbonyl-4-(3-chlorophenyl)-
              2(S)-[2-(2-cyano-5-methoxycarbonylphenoxy)ethyl]-5-oxo-
30   piperazine
        To a solution of 250 mg of methyl 4-cyano-3-hydroxybenzoate (1.42 mmol), as described in Example 4, Step C, and PPh3 (465 mg, 1.77 mmol) in THF (10 mL) was added dropwise a solution of the alcohol from Step E above (503 mg, 1.42 mmol) and DEAD (0.28 mL, 1.77 mmol) in

THF (5 mL). After stirring for 16 hr, the solution was concentrated *in vacuo* and the residue taken up in EtOAc. This was then washed with 10% citric acid solution, saturated NaHCO$_3$ solution, brine and dried over MgSO$_4$. Filtration and removal of the solvent afforded an oil.

5   Column chromatography (silica gel; hexane:EtOAc 4:1) afforded the title compound as a clear oil.

Step G: Preparation of 1-*tert*-butoxycarbonyl-4-(3-chlorophenyl)-
            2(S)-[2-(2-cyano-5-hydroxymethylphenoxy)ethyl]-
10   piperazine

Following the procedure described in Example 1, Step C but using an ester, as described in Step F above, as the starting material, the title compound was obtained.

FAB mass spectrum m/z = 472.21 (M+H requires 471.19)

15

Step H: Preparation of 1-*tert*-butoxycarbonyl-4-(3-chloro-phenyl)-
            2(S)-[2-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-ethyl]-5-
            oxo-piperazine

Following the procedure described in Example 2, Steps D
20   and E but using an alcohol, as described in Step G above, as the starting material, the title compound was obtained as a white solid.

FAB mass spectrum m/z = 522.19 (M+H requires 522.22).

25   Analysis calculated for C$_{28}$H$_{32}$N$_5$O$_3$Cl•0.15CH$_2$Cl$_2$:

C, 63.22; H, 6.09; N, 13.10;

Found: C, 63.17; H, 5.88; N, 12.93.

EXAMPLE 7

30

Preparation of 2-(3-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

Step A: Preparation of 2-(3-chlorophenoxy)-4-methyl-benzonitrile

To a solution of 2-fluoro-4-methylbenzonitrile (356mg, 3.96mmol) and 3-chlorophenol(439μL, 4.16mmol) in 10mL of DMSO was added Cs2CO3 (2.58g, 7.92 mmol). The solution was heated at 80°C for 4h. The solution was diluted with EtOAc and was washed with Sat.
5   NaHCO3 solution, water, and brine. The organics were dried (MgSO4), filtered, and concentrated *in vacuo* to give the title compound without further purification.

Step B: Preparation of 2-(3-chlorophenoxy)-4-bromo-ylmethyl-
10   benzonitrile
                 To a solution of 2-(3-chlorophenoxy)-4-methyl-benzonitrile (640 mg, 2.63 mmol), as described in Step A, NBS (470 mg, 2.63 mmol), and AIBN (13mg, 0.07mmol) in 24mL of CCl4 was refluxed under Ar for 4h. The solution was filtered through a celite pad and the filtrate was
15   concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-6% EtOAc/hexane) to give the title compound.

Step C: Preparation of 2-(3-chlorophenoxy)-4-imidazol-1-ylmethyl-
                 benzonitrile hydrochloride
20   To a solution of 2-(3-chlorophenoxy)-4-bromo-ylmethyl-benzonitrile (111mg, 0.34mmol), as described in Step B, in 10mL of DMF was added imidazole (117mg, 1.72mmol). The reaction was stirred for 18h at ambient temperature. The solvent was removed *in vacuo*, diluted with EtOAc and was washed with saturated NaHCO3 solution, water,
25   and brine. The organics were dried (MgSO4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1% MeOH/CH2Cl2) and treated with 1N HCl in ether to give the title compound as a HCl salt.
^{1}HNMR (CDCl3, 400MHz) d 9.04(1H, s), 7.84(1H, d, J=8Hz), 7.61(2H, d,
30   J=11Hz), 7.43(1H, t, J=8Hz), 7.27(2H, t, J=7Hz), 7.16 (1H, s), 7.05-7.07(2H, m), 5.50(2H, s). FAB MS 310 (M+1)
Anal. calculated for $C_{17}H_{12}N_3O_1Cl_1$ · 1.0 HCl· 0.85 H2O
                 C, 56.47; H, 4.10; N, 11.62;
Found   C, 56.85; H, 4.08; N, 11.23.
35

EXAMPLE 8

Preparation of 2-(4-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-
benzonitrile hydrochloride

5

Step A: Preparation of 2-hydroxy-4-hydroxymethylbenzonitrile

Methyl 4-cyano-3-hydroxybenzoate, as described in Example
4, Step C, (0.50 g, 2.82 mmol) was dissolved in dry THF (30 mL), treated
with LiBH4 (2.0M solution in THF) (5.64 mL, 11.28 mmol) and heated at

10   reflux overnight. The reaction mixture was concentrated, then
partitioned between EtOAc (50 mL) and 1N HCl (50 mL). Next, the
aqueous layer was extracted with additional EtOAc (2 x 50 mL), the
organic layers were combined, washed with brine, and dried (MgSO4).
The title compounds was obtained by filtering and concentrating to

15   dryness.
^{1}H NMR (CD3OD) d 7.45 (1H, d, J = 8 Hz), 6.98 (1H, d, J = 1 Hz), 6.89 (1H,
dd, J = 1, 8, Hz), 4.58 (2H, s).

Step B: Preparation of 4-bromomethyl-2-hydroxy-benzonitrile

20   2-hydroxy-4-hydroxymethylbenzonitrile (0.20 g, 1.34 mmol)
was dissolved in DMF (5 mL) and CH2Cl2 (5 mL) and then treated with
triphenylphosphine (0.53 g, 2.01 mmol) and carbon tetrabromide (0.67 g,
2.01 mmol) at ambient temperature with stirring. After 2 h, the reaction
mixture was partitioned between EtOAc (100 mL) and H2O (100 mL), the

25   organic layer were separated, dried (MgSO4), and filtered to give the title
compound after silica gel chromatography (15% EtOAc/ hexane to
25%EtOAc/ hexane).
^{1}H NMR (CD3OD) d 7.45 (1H, d, J = 8 Hz), 6.94 (1H, s), 6.90 (1H, d, J =8,
Hz), 4.40 (2H, s).

30

Step C: Preparation of 2-hydroxy-4-imidazol-1-ylmethyl-
               benzonitrile

4-bromomethyl-2-hydroxy-benzonitrile (0.22 g, 1.05 mmol)
and imidazole (0.36 g, 5.23 mmol) were dissolved in DMF (10 mL) with

35   stirring at ambient temperature. After stirring for 18 h, the reaction

mixture was concentrated *in vacuo* and purified by silica gel chromatography eluting with 2% $CH_3OH/$ CH_2Cl_2 to 5% $CH_3OH/$ CH_2Cl_2 to give the title compound.

5   ^1H NMR (DMSO) d 11.11 (1H, s), 7.74 (1H, s), 7.58 (1H, d, J = 8 Hz), 7.17 (1H, s), 6.95 (1H, s), 6.74 (1H, d, J =8, Hz), 6.69 (1H, s), 5.23 (2H, s).

Step D: Preparation of 2-(4-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

4-chlorophenethyl alcohol (0.11 g, 0.67 mmol) and
10   triethylamine (0.37 mL, 2.68 mmol) were dissolved in CH_2Cl_2 (5 mL) at 0°C. Then it was treated with methanesulfonyl chloride (0.207 mL, 2.68 mmol), with stirring and warming to ambient temperature, until tlc indicated loss of starting material. The reaction mixture was concentrated *in vacuo*, then dissolved in DMF (1 mL) and added to a
15   mixture of 2-hydroxy-4-imidazol-1-ylmethyl-benzonitrile (0.10 g, 0.50 mmol) and cesium carbonate (0.33 g, 1.0 mmol) in DMF (2 mL). The reaction mixture was heated at 30°C for 18 h, then partitioned between EtOAc and H_2O, the aqueous layer washed with EtOAc, the organic layers combined, washed with brine, and dried (Na_2SO_4). Filtration and
20   concentration to dryness gave the title compound after silica gel chromatography (0.1 to 0.2% CH_3OH/NH_4OH in CH_2Cl_2) and conversion to the hydrochloride salt.

FAB mass spectrum (M+1) 338

Analysis calculated for $C_{19}H_{16}N_3OCl\bullet$ 1.3 HCl $\bullet$ 0.75 H_2O:
25   C, 57.23; H,4.75; N, 10.54;
       Found: C, 57.49; H,4.74; N, 10.14.

Using the procedure described above, but substituting the appropriate heterocycle for imidazole in Step C and the appropriate mesylate or
30   halide in Step D, the following compounds were prepared:

2-(3-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

FAB mass spectrum (M+1) 338
35   Analysis calculated for $C_{19}H_{16}N_3OCl\bullet$ 1.2 HCl $\bullet$ 0.35 H_2O:

C, 58.83; H,4.65; N, 10.83;

Found: C, 58.90; H,4.67; N, 10.50.

2-(2-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

FAB mass spectrum (M+1) 338

2-(phenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

FAB mass spectrum (M+1) 304

Analysis calculated for $C_{19}H_{17}N_3O$ • 1.0 HCl • 0.85 H_2O:

C, 64.25; H, 5.59; N, 11.83;

Found: C, 64.55; H, 5.77; N, 11.44.

2-(3-chlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

FAB mass spectrum (M+1) 324

Analysis calculated for $C_{18}H_{14}ClN_3O$ • 1.2 HCl • 0.40 H_2O:

C, 57.69; H, 4.30; N, 11.21;

Found: C, 57.66; H, 4.31; N, 11.02.

2-(4-chlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

FAB mass spectrum (M+1) 324

2-(2,4-dichlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

FAB mass spectrum (M+1) 358

Analysis calculated for $C_{18}H_{13}Cl_2N_3O$ • 0.10 H_2O:

C, 60.04; H, 3.70; N, 11.67;

Found: C, 60.02; H, 3.84; N, 11.78.

2-(benzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

Analysis calculated for $C_{18}H_{15}N_3O$ • 0.45 H_2O:

C, 72.68; H, 5.39; N, 14.13;

Found: C, 73.03; H, 5.13; N, 13.75.

2-(biphenyl-2-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

FAB mass spectrum (M+1) 366

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Analysis calculated for $C_{24}H_{19}N_3O \bullet$ 1.1 HCl $\bullet$ 0.85 H_2O:

     C, 68.49; H, 5.22; N, 9.99;

Found: C, 68.46; H, 5.24; N, 9.64.

5 <u>2-(phenyl-4-butoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride</u>

FAB mass spectrum (M+1) 332

Analysis calculated for $C_{21}H_{21}N_3O \bullet$ 1.4 HCl:

     C, 65.94; H, 5.90; N, 10.99;

Found: C, 65.94; H, 5.78; N, 10.78.

10

 <u>2-(phenyl-3-propoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride</u>

FAB mass spectrum (M+1) 318

Analysis calculated for $C_{20}H_{19}N_3O \bullet$ 1.1 HCl:

     C, 67.19; H, 5.67; N, 11.75;

15 Found: C, 67.20; H, 5.43; N, 11.70.

2-(biphenyl-4-yl-2-ethoxy)-4-(1,2,4-triazol-1-yl)methyl-benzonitrile <u>hydrochloride</u>

HR mass spectrum theoretical 381.1710; measured 381.1707.

20

2-(biphenyl-4-yl-2-ethoxy)-4-(2-methyl-imidazol-1-yl)methyl-benzonitrile <u>hydrochloride</u>

HR mass spectrum theoretical 394.1910; measured 394.1914.

25 2-(biphenyl-4-yl-2-ethoxy)-4-benzimidazol-1-yl)methyl-benzonitrile <u>hydrochloride</u>

 HR mass spectrum theoretical 430.1920; measured 430.1914.

<div align="center"><u>EXAMPLE 9</u></div>

30

Preparation of 4-imidazol-1-ylmethyl-(2-naphthalen-2-yloxy)-benzonitrile <u>hydrochloride</u>

<u>Step A:</u> <u>Preparation of 4-bromo-3-fluorobenzoic acid</u>

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4-Bromo-3-fluorotoluene(40.0 g, 0.212 mol) was heated at 90°
C in H2O (200 mL) and pyridine (200 mL) with mechanical stirring
under Ar. Potassium permanganate (KMnO4) (67 g, 0.424 mol) was
added portionwise over 3 h. After 4 h, an HPLC of a filtered sample
5   indicated 50 % conversion to the acid. An additional 30 g of KMnO4 was
added and heating continued overnight. HPLC indicated 81%
conversion. Further KMnO4 was added portionwise with reaction
monitoring by HPLC until > 95% conversion was obtained. The reaction
mixture was filtered through Celite, the filter pad washed with H₂O, aq
10   NaOH and EtOH. The filtrate was concentrated to a small volume, then
partitioned between 3N NaOH solution and diethyl ether. The aqueous
basic layer was separated, cooled in an ice- H2O bath and acidified
slowly with 6N HCl solution to precipitate the white solid product. This
was collected by suction filtration and dried at 40 °C. in a vacuum oven
15   overnight to give the title compound. mp 190 -192°C.
^{1}H NMR (CDCl3) d 7.83 (dd, 1H, J = 2, 9 Hz), 7.78 (dd, 1H, J = 2, 8 Hz),
7.67 - 7.71 (m, 1H).

Step B: Preparation of 4-bromo-3-fluorobenzyl alcohol
20   4-Bromo-3-fluorobenzoic acid (40.8 g, 0.187 mol) was
dissolved in THF (250 ml) with magnetic stirring under Ar in an ice-
H2O bath. The cloudy solution was treated dropwise with borane-THF
complex (1 M) (374 mL, 0.374 mol) over a 1 h period maintaining the
internal temperature at < 10°C. The reaction mixture was left to warm
25   to ambient temperature overnight, then cooled in an ice H2O bath and
treated dropwise with H2O (150 mL). The THF was removed on a rotary
evaporator, and the residue partitioned between EtOAc and H2O. The
aqueous layer was extracted with EtOAc (3 x 100 mL), the organic layers
combined, washed with brine, and dried (Na₂SO₄), filtered, and
30   concentrated to give the title compound as an oil which solidified on
standing.
^{1}H NMR (CDCl3) d 7.52 (t, 1H, J = 8 Hz), 7.16 (d, 1H, J = 9 Hz), 7.02 (d,
1H, J = 8 Hz), 4.67 (s, 2H), 1.47 (br s, 1H).

<u>Step C:</u>   <u>Preparation of 2-fluoro-4-hydroxymethylbenzonitrile</u>

4-Bromo-3-fluorobenzyl alcohol(20 g, 0.097 mol) was
dissolved in DMF (100 mL) and then placed under high vacuum for 15
min. The solution was then purged with Ar for 15 min. While purging

5   continued, zinc cyanide (8 g, 0.068 mol) and the catalyst, Pd[(PPh$_3$)]$_4$,
(5.63 g, 0.0049 mol) were added. The reaction mixture was heated at
95°C under Ar for 18 h, then cooled to ambient temperature and added to
H2O. The mixture was extracted with EtOAc, then washed with 1M
HCl, H2O, brine, and dried (Na$_2$SO$_4$). Filtration and concentration to

10   dryness gave the title compound as a white solid after chromatography
(silica gel, hexane: EtOAc, 6.5:3.5.
^{1}H NMR (CDCl3) d 7.61 (t, 1H, J = 8 Hz), 7.23 - 7.29 (m, 2H), 4.80 (d, 2H, J
= 6 Hz), 1.93 (t, 1H, J = 6Hz).

15   <u>Step D:</u>   <u>Preparation of 4-bromomethyl-2-fluoro-benzonitrile</u>

N-Bromosuccinimide (6.6 g, 0.037 mol) was dissolved in
CH$_2$Cl$_2$ (150 mL), cooled to 0°C and treated with dimethylsulfide (3.27
mL, 0.0446 mol). The solution was cooled to -20°C and then treated
dropwise with a solution of 2-fluoro-4-hydroxymethylbenzonitrile (3.74 g,

20   0.0248 mol) in CH$_2$Cl$_2$ (30 mL). After the addition, the reaction mixture
was stirred at 0°C for 2 h then left to warm to ambient temperature
overnight. The reaction mixture was added to ice/ H2O, extracted with
EtOAc, the organic layer separated, washed with brine and dried
(MgSO$_4$). Filtration and concentration to dryness gave the title

25   compound which was purified chromatography (silica gel, 5-10%
EtOAc/ hexane.
^{1}H NMR (CDCl3) d 7.61 (dd, 1H, J = 8, 8 Hz), 7.26 - 7.30 (m, 2H), 4.45 (s,
2H).

30   <u>Step E:</u>   <u>Preparation of 2-fluoro-4-imidazol-1-ylmethyl-benzonitrile</u>

4-Bromomethyl-2-fluoro-benzonitrile (3.44g, 16.0 mmol) and
imidazole (5.47 g, 80.3 mmol) were dissolved in DMF (40 mL) and stirred
at ambient temperature for 2 h. The DMF was removed *in vacuo* and the
residue was partitioned between EtOAc (300 mL) and aqueous saturated

35   NaHCO$_3$ solution. The organic layer was separated, washed with

NaHCO$_3$ solution, H$_2$O, brine, and dried (MgSO$_4$). Filtration and concentration to dryness gave the title compound after chromatography (silica gel, 1-2% CH$_3$OH/CH$_2$Cl$_2$).

^{1}H NMR (CDCl$_3$) d 7.62 (dd, 1H, J = 8.5, 9.5 Hz), 7.57 (s, 1H), 7.16 (s, 1H),

5　　7.00 (d, 1H, J = 8.5 Hz), 6.94 (d, 1H, J = 9.5 Hz), 6.91 (s, 1H), 5.21 (s, 2H).

Step F:　　　Preparation of 2-(2-naphthyloxy)-4-imidazol-1-ylmethyl-
　　　　　　　benzonitrile hydrochloride

　　　　　　　2-Fluoro-4-imidazol-1-ylmethyl-benzonitrile (0.167 g, 0.830

10　mmol), 2-naphthol (0.143 g, 0.996 mmol) and cesium carbonate (0.54 g, 1.66 mmol) were dissolved in DMF (15 mL) and heated at 55°C under Ar for 18 h. The reaction mixture was partitioned between EtOAc and 1N NaOH solution. The organic layer was separated, washed with 1N NaOH solution, H$_2$O, brine, and dried (MgSO$_4$). Filtration and

15　concentration to dryness gave the title compound after chromatography (silica gel, 1% CH$_3$OH/CH$_2$Cl$_2$).

FAB mass spectrum (M+1) 326

Analysis calculated for C$_{21}$H$_{15}$N$_3$O • 1.0 HCl • 0.75 H$_2$O:

　　　　　　　C, 67.19; H, 4.70; N, 11.20;

20　Found:　　　C, 67.23; H, 4.89; N, 11.14.

Using the procedure described above, but substituting the appropriate heterocycle for imidazole in Step E and the appropriate phenol or thiol in Step F, the following compounds were prepared:

25

2-(3-cyanophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

FAB mass spectrum (M+1) 301

2-(3-bromophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

30　FAB mass spectrum (M+1) 353

2-(biphen-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

FAB mass spectrum (M+1) 352

2-(biphen-4-yloxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 352

2-(3-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
5   FAB mass spectrum (M+1) 318

2-(2-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 318

10   2-(3-trifluoromethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 344

2-(3-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 290

15
2-(2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 290

2-(4-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
20   FAB mass spectrum (M+1) 290

2-(3-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 306

25   2-(2-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 306

2-(4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 306
30
2-(3,5-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 304

2-(3,4-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
35   FAB mass spectrum (M+1) 304

2-(3,5-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 336

5   2-(1-naphthyloxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 326

2-(2,4-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 343

10

2-(3-fluorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 294

2-(3-t-butylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
15   FAB mass spectrum (M+1) 332

2-[3-(N,N-diethylamino)phenoxyl-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 347

20   2-(3-N-propylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 318

2-(2,3-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 336

25

2-(2,3-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 304

2-(3,4-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
30   FAB mass spectrum (M+1) 336

2-(2,5-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 336

35   2-(3,4-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

FAB mass spectrum (M+1) 343

<u>2-(2,4-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile</u>
FAB mass spectrum (M+1) 304

5

<u>2-(4-chloro-2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile</u>
FAB mass spectrum (M+1) 324

<u>2-(5-chloro-2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile</u>
10   FAB mass spectrum (M+1) 324

<u>2-(2-chloro-4,5-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile</u>
FAB mass spectrum (M+1) 338

15   2-(5-hydroxymethyl-2-methoxyphenoxy)-4-imidazol-1-ylmethyl-
<u>benzonitrile</u>
FAB mass spectrum (M+1) 336

<u>4-omidazol-1-ylmethyl-2-(3-phenylamino-phenoxy)-benzonitrile</u>
20   FAB mass spectrum (M+1) 367

<u>4-imidazol-1-ylmethyl-2-[3-(2-methylphenylamino)-phenoxy]-benzonitrile</u>
FAB mass spectrum (M+1) 81

25   <u>4-imidazol-1-ylmethyl-2-(3-phenoxy-phenoxy)-benzonitrile</u>
FAB mass spectrum (M+1) 368

<u>2-(2-benzoyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile</u>
FAB mass spectrum (M+1) 380

30

1-(5-chloro-2-methoxy-phenyl)-3-[3-(2-cyano-5-imidazol-1-
<u>ylmethyl-phenoxy)-phenyl]-urea</u>
FAB mass spectrum (M+1) 474

1-(2,5-dimethoxy-phenyl)-3-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-urea
FAB mass spectrum (M+1) 470

5   2-(3-benzyloxy-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 382

2-(4-benzyloxy-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 382

10

2-(2-benzyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 366

2-(3-ethynyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
15   FAB mass spectrum (M+1) 300

2-(4-acetyl-3-methyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 332

20   4-imidazol-1-ylmethyl-2-(1*H*-indazol-6-yloxy)-benzonitrile
FAB mass spectrum (M+1) 315

4-imidazol-1-ylmethyl-2-(5,6,7,8-tetrahydro-naphthalen-1-yloxy)-benzonitrile
25   FAB mass spectrum (M+1) 330

4-imidazol-1-ylmethyl-2-(8-oxo-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-benzonitrile
FAB mass spectrum (M+1) 344

30

4-imidazol-1-ylmethyl-2-(1*H*-indol-7-yloxy)-benzonitrile
FAB mass spectrum (M+1) 315

4-imidazol-1-ylmethyl-2-(3-oxo-indan-4-yloxy)-benzonitrile
35   FAB mass spectrum (M+1) 330

4-imidazol-1-ylmethyl-2-(1*H*-indol-4-yloxy)-benzonitrile
FAB mass spectrum (M+1) 315

5   2-[3-(2-hydroxy-ethoxy)-phenoxy]-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 336

4-imidazol-1-ylmethyl-2-(4-imidazol-1-yl-phenoxy)-benzonitrile
FAB mass spectrum (M+1) 342

10

4'-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-biphenyl-4-carbonitrile
FAB mass spectrum (M+1) 377

N-[3-(2-Cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-acetamide
15   FAB mass spectrum (M+1) 333

4-imidazol-1-ylmethyl-2-(9-oxo-9*H*-fluoren-4-yloxy)-benzonitrile
FAB mass spectrum (M+1) 378

20   2-(5-cyano-2-imidazol-1-ylmethyl-phenoxy)-*N*-phenyl-benzamide
FAB mass spectrum (M+1) 395

2-(5-chloro-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 311

25

N-[3-(2-Cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-
benzenesulfonamide
FAB mass spectrum (M+1) 431

30   4-imidazol-1-ylmethyl-2-(indan-5-yloxy)-benzonitrile
FAB mass spectrum (M+1) 316

2-(9*H*-carbazol-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 365

35

4-imidazol-1-ylmethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-
benzonitrile
FAB mass spectrum (M+1) 330

5   4-imidazol-1-ylmethyl-2-(2-methoxy-4-propenyl-phenoxy)-benzonitrile
FAB mass spectrum (M+1) 346

4-imidazol-1-ylmethyl-2-[4-(3-oxo-butyl)-phenoxy]-benzonitrile
FAB mass spectrum (M+1) 346

10

2-(3-chlorophenoxy)-5-imidazol-1-ylmethyl-benzonitrile hydrochloride
FAB mass spectrum (M+1) 310

2-(4-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride
15   FAB mass spectrum (M+1) 310

2-(3,5-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile
hydrochloride
FAB mass spectrum (M+1) 344

20

2-(pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile dihydrochloride
FAB mass spectrum (M+1) 277

2-(2-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride
25   FAB mass spectrum (M+1) 310

2-(3-chlorophenoxy)-5-(4-phenyl-imidazol-1-ylmethyl)-benzonitrile
hydrochloride
FAB mass spectrum (M+1) 386

30

2-(biphen-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride
Analysis calculated for $C_{23}H_{17}N_3O$ • 1.0 HCl • 0.75 H2O:
            C, 68.82; H, 4.90; N, 10.47;
Found: C, 68.80; H, 4.91; N, 10.30.

35

2-(phenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

Analysis calculated for $C_{17}H_{13}N_3O \cdot 1.0\ HCl \cdot 0.35\ H_2O$:

          C, 64.19; H, 4.66; N, 13.21;

Found: C, 64.33; H, 4.78; N, 12.84.

EXAMPLE 10

Preparation of 2-(2-chloro-4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

Step A: Preparation of 2-(2-chloro-4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

          2-Fluoro-4-imidazol-1-ylmethyl-benzonitrile, as described in Example 9, Step E, (0.118 g, 0.586 mmol), 2-chloro-4-methoxyphenol (0.112 g, 0.703 mmol), KF on alumina (40% by weight) (0.112 g, 0.703 mmol) and 18-crown-6 (0.11 g, 10% by weight of phenol) were dissolved in CH_3CN (5 mL) and heated at reflux under Ar for 18 h. The reaction mixture was filtered, dissolved in CH_3OH and purified by RP HPLC on a Waters Prep Pak column eluting with a 0.1%TFA/H_2O: 0.1%TFA/ CH_3CN gradient (95:5 to 5:95) to give the title compound after conversion to the hydrochloride salt.

FAB mass spectrum (M+1) 340

Analysis calculated for $C_{18}H_{14}ClN_3O_2 \cdot 1.0\ HCl \cdot 0.15\ CH_2Cl_2$:

          C, 56.04; H, 3.96; N, 10.80;

Found: C, 56.25; H, 3.90; N, 10.42.

Using the procedure described above, but substituting the appropriate heterocycle for imidazole (Example 9, Step E) and the appropriate phenol or thiol in Step A, the following compounds were prepared:

2-(2-chlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride

FAB mass spectrum (M+1) 326

4-imidazol-1-ylmethyl-2-(naphthalen-2-ylsulfanyl)-benzonitrile
FAB mass spectrum (M+1) 342

2-(2,4-dichlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile
5 hydrochloride
FAB mass spectrum (M+1) 360

Oxidation of this compound provided the sulfoxide:

10 2-(2,4-dichloro-benzenesulfinyl)-4-imidazol-1-ylmethyl--benzonitrile
FAB mass spectrum (M+1) 376

and the sulfone:

15 2-(2,4-dichloro-benzenesulfonyl)-4-imidazol-1-ylmethyl--benzonitrile
FAB mass spectrum (M+1) 392

2-(2-methyl-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 291
20

2-(2,4-dimethyl-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile
FAB mass spectrum (M+1) 305

2-(4-chloro-2-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile
25 hydrochloride
FAB mass spectrum (M+1) 340

2-(2-chlorophenoxy)-4-(5-methyl-imidazol-1-ylmethyl)-benzonitrile
FAB mass spectrum (M+1) 324
30

2-(2-chlorophenoxy)-4-(4-methyl-imidazol-1-ylmethyl)-benzonitrile
hydrochloride
FAB mass spectrum (M+1) 324

2-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

FAB mass spectrum (M+1) 471

.5   2-(2-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile hydrochloride
FAB mass spectrum (M+1) 318

2-(2,4-dichlorophenoxy)-4-(2-methyl-imidazol-1-ylmethyl)-benzonitrile hydrochloride

10   FAB mass spectrum (M+1) 358

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-benzamide
Analysis calculated for $C_{24}H_{18}N_4O_2$• 0.1 EtOAc:
            C, 72.67; H, 4.70; N, 13.90;
15   Found: C, 72.70; H, 4.70; N, 13.50.

2-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-N-phenyl-acetamide
Analysis calculated for $C_{25}H_{20}N_4O_2$ • 0.95 H2O:
20   C, 70.55; H, 5.19; N, 13.17;
Found: C, 70.52; H, 5.03; N, 12.92.

4-imidazol-1-ylmethyl-2-(quinolin-6-yloxy)-benzonitrile
FAB mass spectrum (M+1) 327

25

4-imidazol-1-ylmethyl-2-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-benzonitrile
FAB mass spectrum (M+1) 343

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-2-phenyl-
30   acetamide
FAB mass spectrum (M+1) 409

5-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-N-cyclohexyl-nicotinamide
FAB mass spectrum (M+1) 402

35

N-(3-chloro-phenyl)-5-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-
nicotinamide

FAB mass spectrum (M+1) 430

5   3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-ethyl-*N*-phenyl-benzamide
FAB mass spectrum (M+1) 423

3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-cyclopropylmethyl-*N*-
phenyl-benzamide

10   FAB mass spectrum (M+1) 449

2-(2,3-dimethoxyphenoxy)-4-(2,4-dimethyl-imidazol-1-ylmethyl)-
benzonitrile hydrochloride

FAB mass spectrum (M+1) 364

15

4-(2-methyl-imidazol-1-ylmethyl)-2-(naphthalen-2-yloxy)-benzonitrile
FAB mass spectrum (M+1) 340

EXAMPLE 11

20

Preparation of 3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-ethyl-*N*-
phenyl-benzamide trifluroacetate

To a solution of 3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-
N-phenyl-benzamide (0.075 g, 0.19 mmol) in DMF (5.0ml) was added

25   NaH (0.016 g, 60% disp., 0.38 mmol). The solution was stirred for 10
min. and iodoethane (0.060 mL, 0.76 mmol) was added and the stirring
continued for 18 hr. The DMF was removed *in vacuo* and the residue
was partitioned with EtOAc and saturated NaHCO$_3$. The EtOAc layer
was washed with H$_2$O, brine, and dried (MgSO$_4$). Filtration and

30   concentration *in vacuo* gave the title compound after purification on
preparative HPLC. FAB mass spectrum m/e 423 (M+1).
Analysis calculated for C$_{26}$H$_{22}$N$_4$O$_2$ • 1.35 TFA • 0.25 H$_2$O :

C, 59.33; H, 4.14; N, 9.65;
Found: C, 59.33; H, 4.11; N, 9.73.

35

Using the procedure described above the following compound was prepared:

3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-cyclopropylmethyl-*N*-phenyl-benzamide

5   FAB mass spectrum m/e 449 (M+1).

EXAMPLE 12

Preparation of 4-(1-imidazol-1-yl-1-methyl-ethyl)-2-(naphthalen-2-yloxy)-
10   benzonitrile hydrochloride

Step A: Preparation of 4-(1-midazol-1-yl-1-methyl-ethyl)-2-
             (naphthalen-2-yloxy)-benzonitrile hydrochloride
             4-Imidazol-1-ylmethyl-2-(naphthalen-2-yloxy)-benzonitrile
15   hydrochloride (126 mg, .348 mmol) was dissolved in dry THF (2 mL) and
cooled to -78°C under argon. Lithium bis(trimethylsilyl)amide (1.31 mL,
1.31 mmol) was added dropwise over 5 min and stirred for 15 min.
Methyl iodide (.086 mL, 1.39 mmol) was added and the mixture stirred at
-78°C for 4 h. The reaction was quenched with sat. NaHCO$_3$ solution (1
20   mL), warmed to RT, diluted with sat. NaHCO$_3$ solution and extracted
with CH$_2$Cl$_2$ (3X). The combined organic layers were dried (Na$_2$SO$_4$),
concentrated, and purified using SiO$_2$ chromatography (0.5 - 1.0 %
MeOH/CH$_2$Cl$_2$). The oil was dissolved in CH$_2$Cl$_2$ and treated with 1N
HCl ethereal solution to give the title compound.
25

EXAMPLE 13

Preparation of 1-[4-iodo-3-(naphthalen-2-yloxy)-benzyl]-1*H*-imidazole

30   Step A: Preparation of 4-iodo-3-(naphthalen-2-yloxy)-benzoic acid
             methyl ester
             A mixture of 3-hydroxy-4-iodo-benzoic acid acid methyl
ester (0.505 g, 1.82 mmol), cupric acetate (0.330 g, 1.82 mmol), 2-
naphthylboronic acid (0.625 g, 3.63 mmol) and powdered 4A molecular
35   sieves (0.3 g) in CH$_2$Cl$_2$ (21 mL) was treated with triethylamine (1.27 mL,
9.08 mmol) and stirred at ambient temperature for 18 hr. The reaction

mixture was filtered through celite, concentrated to dryness and chromatographed (SiO₂, 5 - 40% EtOAc: hexane) to give the title compound. FAB mass spectrum (M+1) 405.

5   Step B: Preparation of [4-iodo-3-(naphthalen-2-yloxy)-phenyl]-
                 methanol
                 4-Iodo-3-(naphthalen-2-yloxy)-benzoic acid methyl ester
(0.10 g, 0.25 mmol) dissolved in THF (2 mL) was treated with LiBH₄ (2 M
solution in THF) (0.247 mL, 0.495 mmol) and heated at reflux for 1.5 hr.
10 The reaction mixture was cooled, added to H₂O (50 mL)- concd HCl (4.3
mL), and extracted with EtOAc (3x30 mL). The organics were
combined, washed with H₂O, aq saturated NaHCO₃ solution, brine, and
dried (Na₂SO₄). Filtration and concentration to dryness gave the title
compound which was used without purification.
15

    Step C: Preparation of [4-iodo-3-(naphthalen-2-yloxy)-phenyl]-
                 methyl bromide
                 To a solution of [4-iodo-3-(naphthalen-2-yloxy)-phenyl]-
methanol (0.085 g, 0.226 mmol) in CH₂Cl₂ (2 mL) at -15°C was added a
20 cold (0°C) solution of N-bromosuccinimide (0.120 g, 0.68 mmol) in
dimethyl sulfide (0.060 mL, 0.814 mmol) with stirring. The reaction
mixture was allowed to warm to ambient temperature overnight,
concentrated to dryness, and chromatographed (SiO₂,
10%EtOAc:hexane) to give the title compound which was used without
25 purification.

    Step D: Preparation of 1-[4-Iodo-3-(naphthalen-2-yloxy)-benzyl]-1*H*-
                 imidazole
                 [4-Iodo-3-(naphthalen-2-yloxy)-phenyl]-methyl bromide
30 (0.226 mmol) and imidazole (0.10 g) were dissolved in DMF (2 mL) and
stirred at ambient temperature for 18 hr. The reaction mixture was
purified by RP LC on a Vydac column eluting with a gradient of
0.1%TFA/H₂O: 0.1%TFA/CH₃CN (95/5:5/95) to give the title compound.
FAB mass spectrum (M+1) 427.
35 Analysis calculated for C₂₀H₁₅ IN₂O • 0.35 Et₂O • 0.25 HCl:

C, 55.71; H, 4.10; N, 6.07;
Found: C, 55.70; H, 4.07; N, 5.70.

EXAMPLE 14

Preparation of acetic acid 3-[3-(2-chloro-phenoxy)-4-cyano-benzyl]-3H-
imidazol-4-ylmethyl ester hydrochloride

Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-
imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride
(35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added
triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the
solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF
was added dropwise. The reaction mixture was stirred for 20 hours,
poured over ice, filtered, and washed with ice water. The resulting
product was slurried with cold dioxane, filtered, and dried *in vacuo* to
provide the title product as a white.

Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-
imidazole

1-Triphenylmethyl-4-(hydroxymethyl)-imidazole (260 mmol)
was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780
mmol) was added dropwise, and the reaction was stirred for 48 hours
during which it became homogeneous. The solution was poured into 2 L
of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq.
NaHCO3, and brine, then dried (Na2SO4), filtered, and concentrated *in
vacuo* to provide the title product as a white powder which was
sufficiently pure for use in the next reaction.

Step C: Preparation of 1-(4-cyano-3-fluorobenzyl)-5-(acetoxymethyl)-
imidazole hydrobromide

A solution of 1-triphenylmethyl-4-(acetoxymethyl)imidazole
(36.72 g, 96.14 mmol) and 4-bromomethyl-2-fluoro-benzonitrile, as
described in Example 9, Step D), (20.67 g, 96.14 mmol) in 250 mL of

EtOAc was stirred at 60 °C for 20 hours, during which a white
precipitate formed. The reaction was cooled to room temperature and
filtered to provide the solid imidazolium bromide salt. The filtrate was
concentrated *in vacuo* to a volume of 100 mL, reheated at 60 °C for two
5   hours, cooled to room temperature, and filtered again. The filtrate was
concentrated *in vacuo* to a volume 40 mL, reheated at 60 °C for another
two hours, cooled to room temperature, and concentrated *in vacuo* to
provide a pale yellow solid. All of the solid material was combined,
dissolved in 300 mL of methanol, and warmed to 60 °C. After two hours,
10   the solution was reconcentrated *in vacuo* to provide a white solid which
was triturated with hexane to remove soluble materials. Removal of
residual solvents *in vacuo* provided the title product hydrobromide as a
white solid.

15   Step D: Preparation of acetic acid 3-[3-(2-chloro-phenoxy)-4-cyano-
                    benzyl]-3H-imidazol-4-ylmethyl ester hydrochloride
                    To a solution of 1-(4-cyano-3-fluorobenzyl)-5-(acetoxymethyl)-
imidazole hydrobromide (0.29 g, 1.06 mmol) in DMF (7.0 mL) was added
2-chlorophenol (0.132 mL, 1.27 mmol) and cesium carbonate (0.691 g,
20   2.12 mmol). The mixture was heated to 55°C and stirred for 18 hr. The
DMF was removed *in vacuo* and the residue was partitioned with EtOAc
and saturated NaHCO$_3$ solution. The EtOAc layer was washed with
H$_2$O, brine, and dried (MgSO$_4$). Filtration and concentration to dryness
gave the title compound after chromatography (SiO$_2$, CH$_2$Cl$_2$:CH$_3$OH:
25   NH$_4$OH/ 98:2:0.2) and conversion to the hydrochloride salt.
FAB mass spectrum m/e 382 (M+1).
Analysis calculated for C20H16ClN3O3 • 1.4 HCl :
Found: C, 55.50; H, 4.05; N, 9.71.
             C, 55.55; H, 4.07; N, 9.41.
30

EXAMPLE 15

Preparation of 2-(2-chloro-phenoxy)-4-(5-hydroxymethyl-imidazol-1-
ylmethyl)-benzonitrile hydrochloride

To a solution of acetic acid 3-[3-(2-chloro-phenoxy)-4-cyano-benzyl]-3H-imidazol-4-ylmethyl ester hydrochloride (as described in Example 14) (0.112 g, 0.268 mmol) in THF (2.0 mL) was added 1M NaOH (0.536 mL). After 3.5 hr. the reaction was partitioned between EtOAc

5   and saturated NaHCO$_3$ solution. The EtOAc layer was washed with H$_2$O, brine, and dried (MgSO$_4$). Filtration and concentration *in vacuo* gave the title compound after conversion to the hydrochloride salt. FAB mass spectrum m/e 340 (M+1).
Analysis calculated for C$_{18}$H$_{14}$ClN$_3$O$_2$ • 1.0 HCl • 0.2 EtOAc :

10   C, 57.33; H, 4.25; N, 10.67.
Found: C, 57.68; H, 3.83; N, 10.65.

EXAMPLE 16

15 Preparation of 4-(5-aminomethyl-imidazol-1-ylmethyl)-2-(2-chloro-phenoxy)-benzonitrile ditrifluroacetate

Step A: Preparation of 4-(5-azidomethyl-imidazol-1-ylmethyl)-2-(2-chloro-phenoxy)-benzonitrile

20   To a solution of 2-(2-chloro-phenoxy)-4-(5-hydroxymethyl-imidazol-1-ylmethyl)-benzonitrile hydrochloride, as described in Example 15, (0.07 g, 0.186 mmol) in CH$_2$Cl$_2$ (4.0 mL), and triethylamine (0.078 mL, 0.558 mmol) at 0°C was added methanesulfonyl chloride (0.016 mL, 0.205 mmol). The cooling bath was removed and the mixture

25 was stirred for 1hr. To this solution was added sodium azide (0.018 g, 0.277 mmol) in DMF (1.0 mL). After 1hr. the reaction mixture was partitioned between EtOAc and saturated NaHCO$_3$ solution. The EtOAc layer was washed with H$_2$O, brine, and dried (MgSO$_4$). Filtration and concentration *in vacuo* gave the title product which was used in the next

30 step without further purification.

Step B: Preparation of 4-(5-aminomethyl-imidazol-1-ylmethyl)-2-(2-chloro-phenoxy)-benzonitrile ditrifluroacetate
                     To a solution of 4-(5-azidomethyl-imidazol-1-ylmethyl)-2-(2-

35 chloro-phenoxy)-benzonitrile (0.05 g, 0.137 mmol) in CH$_3$OH (5.0 mL)

under argon was added 10% Pd/C (0.020 g). The mixture was placed under 1 atmosphere of hydrogen and stirred for 18 hr. The mixture was filtered and the CH₃OH was removed *in vacuo* to give the title compound after purification by preparative HPLC.

5   FAB mass spectrum m/e 339 (M+1).

Analysis calculated for $C_{18}H_{15}ClN_4O$ • 2.2 HCl • 0.1 H_2O :

C, 45.49; H, 2.97; N, 9.47.

Found: C, 45.43; H, 2.92; N, 9.50.

10   <u>EXAMPLE 17</u>

Preparation of N-{3-[4-cyano-3-(2,3-dimethoxy-phenoxy)-benzyl]-3H-imidazol-4-ylmethyl]-2-cyclohexyl-acetamide hydrochloride

15   <u>Step A:</u>   Preparation of 1-(4-cyano-3-fluorobenzyl)-5-(hydroxymethyl)imidazole

To a solution of 1-(4-cyano-3-fluorobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide (as described in Example 14, Step C) (31.87 g, 89.77 mmol) in 300 mL of 2:1 THF/water at 0 °C was added lithium

20   hydroxide monohydrate (7.53 g, 179 mmol). After two hours, the reaction was concentrated *in vacuo* to a 100 mL volume, stored at 0 °C for 30 minutes, then filtered and washed with 700 mL of cold water to provide a brown solid. This material was dried *in vacuo* over P_2O_5 to provide the titled product as a pale brown powder which was sufficiently

25   pure for use in the next step without further purification.

<u>Step B:</u>   Preparation of 4-(5-aminomethyl-imidazol-1-ylmethyl)-2-fluoro-benzonitrile dihydrochloride

Following the procedures described in Example 16 but

30   starting with 1-(4-cyano-3-fluorobenzyl)-5-(hydroxymethyl)imidazole (1.1 g, 4.85 mmol) the title compound was prepared.

<u>Step C:</u>   Preparation of N-[3-(4-cyano-3-fluoro-benzyl)-3H-imidazol--ylmethyl]-2-cyclohexyl-acetamide

To a solution of 4-(5-aminomethyl-imidazol-1-ylmethyl)-2-
fluoro-benzonitrile dihydrochloride (0.17 g, 0.651 mmol) in DMF (5.0 mL)
was added cyclohexylacetic acid (0.11 g, 0.782 mmol), BOP reagent (0.433
g, 0.977 mmol), and NMM (0.28 mL, 2.6 mmol). The mixture was
5   stirred for 18 hr. The DMF was removed *in vacuo* and the residue was
partitioned with EtOAc and saturated NaHCO₃ solution. The EtOAc
layer was washed with H₂O, brine, and dried (MgSO₄). Filtration and
concentration *in vacuo* gave the title compound after chromatography
(silica gel, CH₂Cl₂:CH₃OH:NH₄OH/ 97:3:0.3).

10

Step D: Preparation of N-{3-[4-cyano-3-(2,3-dimethoxy-phenoxy)-
             benzyl]-3H-imidazol-4-ylmethyl}-2-cyclohexyl-acetamide
             hydrochloride   )

To a solution of N-[3-(4-cyano-3-fluoro-benzyl)-3H-imidazol-
15   ylmethyl]-2-cyclohexyl-acetamide (0.16 g, 0.451 mmol) in acetonitrile (7.0
mL) was added 2,3-dimethoxyphenol (0.065 mL, 0.497 mmol), KF/Al₂O₃
(0.2 g), and 18-crown-6 (0.032 g). The mixture was refluxed for 20 hr.
The acetonitrile was removed *in vacuo* and the residue was partitioned
with EtOAc and saturated NaHCO₃. The ethyl acetate layer was washed
20   with H2O, brine, and dried (MgSO₄). Removal of the ethyl acetate *in
vacuo* gave the title compound after chromatography (silica gel,
CH₂Cl₂:CH₃OH:NH₄OH / 98:2:0 and conversion to the hydrochloride salt.
FAB mass spectrum m/e 489 (M+1).

25   EXAMPLE 18

Preparation of 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-imidazol-1-yl-
methyl]-benzonitrile trifluoroacetate

30   Step A: Preparation of 4-Bromo-3-fluorobenzaldehyde
             To a well-stirred mixture of 4-bromo-3-fluorobenzyl alcohol
(as described in Example 9, Step B) (10.25 g, 0.05 mol), TEMPO (0.781 g,
0.005 mol) and tetrabutylammonium fluoride (1.39 g, 0.005 mol) in
CH₂Cl₂ (200 mL) and a solution of 0.5M NaHCO₃/ 0.05M K₂CO₃ (200 mL)
35   was added N-chlorosuccinimide (9.35 g, 0.07 mol). After 6 hrs, the

layers were separated, the aqueous layer back-washed with CH_2Cl_2 (2 x 50 mL), the organics combined and dried (Na_2SO_4). The solution was filtered, concentrated to half its volume, then chromatographed (silica gel, CH_2Cl_2) to give the title compound.

5 ^1H NMR ($CDCl_3$) δ 9.96 (s, 1H), 7.78 (dd, 1H, J = 2, 8 Hz), 7.62 (dd, 1H, J = 2, 8 Hz), 7.56 (dd, 1H, J = 2, 8 Hz).

Step B: Preparation of (4-bromo-3-fluoro-phenyl)-(4-chloro-phenyl)-methanol

10   To a solution of 4-bromo-3-fluorobenzaldehyde (1.6 g, 7.88 mmol) in diethylether (20 mL) at 0°C was added 4-chlorophenyl-magnesiumbromide (1M/ether, 9.46 mL, 9.46 mmol) dropwise via syringe. The cooling bath was removed and after the mixture was stirred for 18 hr it was cooled to 0°C and saturated NH_4Cl solution (20 15 mL) was added to quench the reaction. The reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc layer was washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave the title compound as a solid after chromatography (silica gel, hexane:EtOAc/ 85:15).

20

Step C: Preparation of (4-cyano-3-fluoro-phenyl)-(4-chloro-phenyl)-methanol

Following the procedure described in Example 9, Step C, but starting with (4-bromo-3-fluoro-phenyl)-(4-chloro-phenyl)-methanol (2.2 25 g, 6.97 mmol), the title compound was obtained as a solid.

Step D: Preparation of 4-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-2-fluoro-benzonitrile

To a solution of (4-cyano-3-fluoro-phenyl)-(4-chloro-phenyl)-30 methanol (2.2 g, 8.79 mmol) in acetonitrile (30 mL) was added CDI (4.28 g, 8.79 mmol) and imidazole hydrochloride (2.75 g, 8.79 mmol) and the mixture was heated at reflux for 3 hr. The acetonitrile was removed *in vacuo* and the residue was partitioned with EtOAc and saturated $NaHCO_3$ solution. The EtOAc layer was washed with H_2O, brine, and

dried (MgSO$_4$). Filtration and concentration *in vacuo* gave the title compound.

Step E: Preparation of 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-benzonitrile trifluoroacetate

Following the procedure described in Example 11, Step A, but starting with 4-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-2-fluoro-benzonitrile, as described in Step D, (0.06 g, 0.193 mmol) and 3-chlorophenol (0.022 mL, 0.212 mmol), the the title compound was obtained after purification by preparative HPLC.

FAB mass spectrum m/e 420 (M+1).

Analysis calculated for C$_{23}$H$_{15}$Cl$_2$N3O • 1.90 TFA • 0.40 H$_2$O :

           C, 49.98; H, 2.77; N, 6.52.

Found: C, 49.98; H, 2.72; N, 6.36.

EXAMPLE 19

Preparation of 2-(3-chloro-phenoxy)-4-[1-(4-chloro-phenyl)-2-hydroxy-1-imidazol-1-yl-ethyl]-benzonitrile hydrochloride

To a solution of 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-benzonitrile trifluoroacetate (0.065 g, 0.122 mmol) in acetonitrile (5 mL) was added 1M KOH (0.5 mL) (pH = 9-10) and 37% aqueous formaldehyde (0.14 mL) After stirring for 18hr the mixture was adjusted to pH = 3 with acetic acid, diluted with CH$_3$OH (3 mL) and purified on prep HPLC. The TFA salt was converted to the HCl salt to obtain the title compound.

FAB mass spectrum m/e 450 (M+1).

Analysis calculated for C$_{24}$H$_{17}$Cl$_2$N3O$_2$• 0.4 CH$_2$Cl$_2$ • 0.3 H$_2$O :

           C, 57.13; H, 3.75; N, 8.06.

Found: C, 57.13; H, 3.82; N, 7.67.

EXAMPLE 20

Preparation of 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-hydroxy-(3*H*-imidazol-4-yl)-methyl]-benzonitrile

5

Step A: Preparation of (4-bromo-3-fluoro-phenyl)-(4-chlorophenyl)-methanol

4-Bromo-3-fluorobenzaldehyde (as described in Example 18, Step A) (3.61 g, 17.7 mmol) was dissolved in anhydrous diethyl ether (40

10   mL). To this solution was added a 1.0M solution of 4-chlorophenyl-magnesium bromide (21.3 mL, 21.3 mmol). After stirring at ambient temperature for 4hr the reaction was quenched with satd. NH$_4$Cl and extracted with Et$_2$O. The organic layer was washed with satd NaHCO$_3$ solution, water, brine, dried (MgSO$_4$), concentrated and purified by

15   chromatography (SiO$_2$, 10% EtOAc/hexane) to give the title compound.

Step B: Preparation of (4-bromo-3-fluoro-phenyl)-(4-chloro-phenyl)-methanone

(4-Bromo-3-fluoro-phenyl)-(4-chloro-phenyl)-methanol (2.26

20   g, 7.16 mmol) and MnO$_2$ (6.22g, 70.1 mmol) was stirred in CH$_2$Cl$_2$ (40 mL) for 40 hr. The solution was filtered through a celite pad and concentrated to give the title compound.

Step C: Preparation of (4-bromo-3-fluoro-phenyl)-(4-chloro-phenyl)-

25   (1-trityl-1*H*-imidazol-4-yl)-methanol

4-Iodo-1-trityl-1*H*-imidazole (1.39 g, 3.18 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (10 mL). To this solution was added a 3.0M solution of ethylmagnesium bromide (1.11 mL, 3.34 mmol) and stirred under Ar. After 3hr, a solution of (4-bromo-3-fluoro-phenyl)-(4-

30   chloro-phenyl)-methanone (1.00g, 3.18 mmol) dissolved in CH$_2$Cl$_2$ (5 mL) was added dropwise and the resulting solution was stirred overnight. The reaction was quenched with satd. NH$_4$Cl solution, diluted with satd. NaHCO$_3$ solution to pH=8.5, and extracted with CH$_2$Cl$_2$ (3X). The combined organic layers were dried (MgSO$_4$), concentrated and purified

using SiO$_2$ chromatography (10-20% EtOAc/Hexane) to yield the title compound.

Step D: Preparation of 4-[(4-chloro-phenyl)-hydroxy-(1-trityl-1H-imidazol-4-yl)-methyl]-benzonitrile

(4-Bromo-3-fluoro-phenyl)-(4-chloro-phenyl)-(1-trityl-1H-imidazol-4-yl)-methanol (0.360 g, 0.578 mmol) and Zn(CN)$_2$ (0.045 g, 0.405 mmol) was stirred in anhydrous DMF (8 mL). The solution was purged with Ar for 10 min, degassed under high vacuum for 5 min, then tetrakis(triphenylphosphine)palladium(0) (0.067 mg, 0.057 mmol) was added and the mixture stirred overnight at 80°C under Ar. Subsequent additions of Zn(CN)$_2$ and tetrakis(triphenylphosphine)palladium(0) were added to drive the reaction to completion. The reaction was diluted with EtOAc and extracted with satd. NaHCO$_3$ solution, water and brine, dried (MgSO$_4$), concentrated and purified using SiO$_2$ chromatography (0.5% MeOH/CH$_2$Cl$_2$) to yield the title compound.

Step E: Preparation of 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-hydroxy-(1-trityl-1H-imidazol-4-yl)-methyl]-benzonitrile

4-[(4-Chloro-phenyl)-hydroxy-(1-trityl-1H-imidazol-4-yl)-methyl]-2-fluoro-benzonitrile (0.337 g, 0.591 mmol), 3-chlorophenol (0.074 mL, 0.709 mmol), 40% KF on alumina (0.182 g), and 18-Crown-6 ether (0.018 g, 0.068 mmol) were refluxed in CH$_3$CN for 40 hr under Ar. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc, washed with satd. NaHCO$_3$ solution, water, brine and dried (MgSO$_4$). Filtration and concentration gave the title compound.

Step F: Preparation of 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-hydroxy-(3H-imidazol-4-yl)-methyl]-benzonitrile

2-(3-Chloro-phenoxy)-4-[(4-chloro-phenyl)-hydroxy-(1-trityl-1H-imidazol-4-yl)-methyl]-benzonitrile (0.269 g, 0.396 mmol), trifluoroacetic acid (5 mL), triethylsilane (0.050 mL, 3.17 mmol) was stirred in CH$_2$Cl$_2$ (5 mL) under Ar for 2hr. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc, washed with satd. NaHCO$_3$ solution, water, brine, dried (MgSO$_4$), concentrated and purified using

SiO$_2$ chromatography (1-1.5% MeOH/CH$_2$Cl$_2$ w NH$_4$OH) to give the title
compound. FAB MS (M+1) = 436
Analysis calculated for C$_{23}$H$_{15}$Cl$_2$N$_3$O$_2$ • 0.35 H$_2$O :

            C, 62.41; H, 3.58; N, 9.49.
5   Found: C, 62.38; H, 3.68; N, 9.28.

EXAMPLE 21

Preparation of 2-(2,4-dichloro-phenylsulfanyl)-4-[5-(2-morpholin-4-yl-
10   ethyl)-imidazol-1-ylmethyl]-benzonitrile

      Step A: Preparation of {2-[3-(4-cyano-3-fluoro-benzyl)-3H-imidazol-
                   4-yl]-ethyl}-carbamic acid tert-butyl ester
                   To a solution of N$^\Gamma$-pivaloyloxymethyl-N$^\alpha$-phthaloyl-
15   histamine (J. C. Emmett, F. H. Holloway, and J. L. Turner, *J. Chem.
     Soc., Perkin Trans. 1*, 1341, (1979)) (4.59 g, 0.0124 mmol) in acetonitrile
     (40 mL) was added 2-fluoro-4-imidazol-1-ylmethyl-benzonitrile (as
     described in Example 9, Step D) (2.8 g, 0.013 mmol) and the mixture was
     heated to reflux for 18 hr. A white solid precipitate formed which after
20   cooling to 0°C was collected by filtration to obtain the quaternary salt.
     This intermediate was dissolved in EtOH (100 mL), hydrazine (1.46 mL,
     0.046 mmol) was added, and the mixture was heated at reflux for 4 hr.
     A white precipitate was observed and the reaction was cooled to 25°C.
     Dimethylphthalate (11.4 mL, 0.0699 mmol) was added and the mixture
25   was again refluxed for 18 hr. After cooling to 25°C the precipitate was
     removed by filtration and washed with EtOAc. The filtrate was
     evaporated *in vacuo* and the residue was dissolved in THF (125 mL) and
     H$_2$O (25 mL). To this solution was added solid Na$_2$CO$_3$ (4.0 g, 0.0377
     mmol) and BOC$_2$O (4.47 g, 0.020 mmol) and the reaction was stirred for
30   18 hr. The THF was removed *in vacuo* and the mixture was partitioned
     with EtOAc and saturated NaHCO$_3$. The EtOAc layer was washed with
     brine, dried with MgSO$_4$, and evaporated *in vacuo* to obtain the title
     product after chromatography (silica gel, CH$_2$Cl$_2$:MeOH:NH$_4$OH/
     97:3:0.3.

35

<u>Step B:</u>   Preparation of 4-[5-(2-amino-ethyl)-imidazol-1-ylmethyl]-2-
                     fluoro-benzonitrile dihydrochloride

                     A solution of {2-[3-(4-cyano-3-fluoro-benzyl)-3H-imidazol-4-
yl]-ethyl}-carbamic acid tert-butyl ester (1.0 g, 0.0029 mmol) in EtOAc (30
5   mL) was cooled to -20°C and saturated with HCl gas. The cooling bath
was removed and the reaction was stirred for 2 hr. The solvent was
removed *in vacuo* to obtain the title compound which was used without
further purification.

10   <u>Step C:</u>   Preparation of 2-fluoro-4-[5-(2-morpholin-4-yl-ethyl)-
                     imidazol-1-ylmethyl]-benzonitrile

                     To a solution of 4-[5-(2-amino-ethyl)-imidazol-1-ylmethyl]-2-
fluoro-benzonitrile dihydrochloride (0.92 g, 0.0029 mmol) in acetonitrile
(150 mL) and triethylamine (3.2 mL) was added 2-bromoethyl ether (0.839
15   mL, 0.0067 mmol) and the mixture was refluxed for 48 hr. The solvents
were removed *in vacuo* and the residue was dissolved in EtOAc which
was washed twice with 1M HCl (100 mL). The HCl layers were
combined and adjusted to pH = 9 with solid Na_2CO_3 and extraxcted 3
times with EtOAc. The EtOAc layers were combined and dried with
20   brine and MgSO4. Removal of the EtOAc *in vacuo* yielded the title
compound which was used as is in the next step.

Step D: Preparation of 2-(2,4-dichloro-phenylsulfanyl)-4-[5-(2-
                     morpholin-4-yl-ethyl)-imidazol-1-ylmethyl]-benzonitrile
25   Following the procedure described in Example 11, Step A,
the title compound was prepared using 2-fluoro-4-[5-(2-morpholin-4-yl-
ethyl)-imidazol-1-ylmethyl]-benzonitrile (0.15 g, 0.477 mmol) and 2,4-
dichlorothiophenol (0.086 g, 0.477 mmol).
     FAB mass spectrum m/e 473 (M+1).
30   Analysis calculated for $C_{23}H_{22}Cl_2N_4OS$ • 0.85 TFA • 0.3 H_2O :
                     C, 51.52; H, 4.11; N, 9.73.
     Found: C, 51.51; H, 4.29; N, 9.36.

     Following the above methods, the following compound was prepared:
35

2-(2,4-dichloro-phenoxy)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-
ylmethyl]-benzonitrile

FAB mass spectrum m/e 457 (M+1).

Analysis calculated for $C_{23}H_{22}Cl_2N_4O_2 \cdot 0.4\ H_2O$:

        C, 59.34; H, 4.96; N, 12.04.

Found: C, 59.32; H, 4.89; N, 11.75.

EXAMPLE 22

Preparation of 4-[hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-2-
(naphthalen-2-yloxy)-benzonitrile hydrochloride

Step A: Preparation of 2-Fluoro-4-formylbenzonitrile

    2-Fluoro-4-hydroxymethylbenzonitrile (Example 9, Step C)
10 g, 0,066 mol) and triethylamine (32.3 mL, 0.231 mol) were dissolved in
CH_2Cl_2 (100 mL)- DMSO (20 mL) at < 5°C. with stirring and treated
dropwise with a solution of pyridine•SO_3 complex (31.5 g, 0.198 mol) in
DMSO (70 mL) maintaining the reaction mixture temperature at <10°C.
The reaction mixture was stirred at 5°C for 1 hr after the addition, then
at 20°C. for 1 hr, then partitioned between CH_2Cl_2 and H_2O. The organic
layer was separated, washed well with H_2O, brine, and dried (Na_2SO_4).
Filtration and concentration gave the title compound after purification
by chromatography (silica gel, hexane: EtOAc, 3:1).

^{1}H NMR (CDCl3) δ 10.06 (d, 1H, J = 2 Hz), 7.86 (dd, 1H, J = 5,8 Hz), 7.798
(dd, 1H, J = 1, 8 Hz), 7.728 (dd, 1H, J = 1, 8 Hz).

Step B: Preparation of 2-fluoro-4-[hydroxy-(1-trityl-1H- imidazol-
4-yl)-methyl]-benzonitrile

    To a solution of 4-iodo-1-trityl-1H-imidazole (5.00 g, 11.5
mmol) in anhydrous CH_2Cl_2 (30 mL) was added a 3.0M solution of
ethylmagnesium bromide (6.58 mL, 19.7 mmol) with stirring under Ar.
After 3h, the reaction mixture was cooled to -78°C and a solution of 2-
fluoro-4-formyl-benzonitrile (1.70g, 11.5 mmol) dissolved in CH_2Cl_2 (20
mL) was added dropwise. The reaction was allowed to warm to RT over
2h, quenched with saturated NH_4Cl solution, diluted with satd. $NaHCO_3$

solution to pH=8.5, and extracted with CH$_2$Cl$_2$ (3X). The combined organic layers were dried (MgSO$_4$), concentrated and purified using SiO$_2$ chromatography (0-1% MeOH/CH$_2$Cl$_2$) to yield the title compound.

5   Step C: Preparation of acetic acid (4-cyano-3-fluoro-phenyl)-(1-trityl-
1*H*-imidazol-4-yl)-methyl ester
2-Fluoro-4-[hydroxy-(1-trityl-1*H*-imidazol-4-yl)-methyl]-
benzonitrile (4.05 g, 8.81 mmol), pyridine (2.14 mL, 26.4 mmol), and
acetic anhydride (12.5 mL, 132 mmol) were stirred in anhydrous DMF
10   (60 mL) for 3h under Ar. The reaction was concentrated *in vacuo*,
diluted with EtOAc (250 mL), washed with H$_2$O (2X), brine, dried
(MgSO$_4$) and concentrated to give the title compound.

Step D: Preparation of acetic acid (4-cyano-3-fluoro-phenyl)-(3-
15   methyl-3*H*-imidazol-4-yl)-methyl ester
Acetic acid (4-cyano-3-fluoro-phenyl)-(1-trityl-1*H*-imidazol-
4-yl)-methyl ester (4.60 g, 9.17 mmol) and dimethyl sulfate (0.83 mL, 8.81
mmol) were dissolved in EtOAc (20 mL) and heated at 60°C overnight
under Ar. The reaction was concentrated *in vacuo*, diluted with MeOH
20   (30 mL), and refluxed for 1h. Concentrated *in vacuo* and purified using
SiO$_2$ chromatography (0.5 - 4% MeOH/CH$_2$Cl$_2$ with NH$_4$OH) to give the
title compound.

Step E: Preparation of 2-fluoro-4-[hydroxy-(3-methyl-3H-imidazol-
25   4-yl)-methyl]-benzonitrile
Acetic acid (4-cyano-3-fluoro-phenyl)-(3-methyl-3*H*-
imidazol-4-yl)-methyl ester (1.26 g, 4.59 mmol) and NaOH (5.5 mL, 5.5
mmol) were dissolved in THF (15 mL) and H$_2$O (25 mL). After 1h, the
reaction was diluted with satd. NaHCO$_3$ solution, extracted with CH$_2$Cl$_2$
30   (3X), dried (MgSO$_4$) and concentrated to give the title compound.

Step F: Preparation of 4-[hydroxy-(3-methyl-3*H*-imidazol-4-yl)-
methyl]-2-(naphthalen-2-yloxy)-benzonitrile hydrochloride
2-Fluoro-4-[hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-
35   benzonitrile (0.099 g, 0.428 mmol), 2-naphthol (0.062 g, 0.4287 mmol) and

Cs_2CO_3 (0.279 g, 0.856 mmol) were dissolved in anhydrous DMSO (5 mL) and heated at 80°C under Ar for 1.5h. The reaction was diluted with EtOAc, washed with satd. $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$), concentrated and purified using SiO_2

5   chromatography (1-2.5% MeOH/CH2Cl2). The purified compound was dissolved in CH_2Cl_2 and treated with 1N HCl ethereal solution to give the title compound.

FAB MS (M+1) = 365.

Analysis calculated for $C_{22}H_{17}N_3O_2$ • 1.00 HCl • 1.60 H_2O:

10   C, 62.81; H, 5.08; N, 9.99

Found: C, 62.81; H, 4.98; N, 10.20.

EXAMPLE 23

15   Preparation of 4-[amino-(3-methyl-3H-imidazol-4-yl)-methyl]-2-(naphthalen-2-yloxy)-benzonitrile

4-[Hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-2-(naphthalen-2-yloxy)-benzonitrile (as described in Example 22) (0.219 g, 0.616 mmol) was dissolved in $SOCl_2$ (5 mL) and stirred at RT for 2h

20   under Ar_2. The solution was concentrated *in vacuo* and azeotroped with CH_2Cl_2 (3X). The solid was dissolved in $CHCl_3$ (20 mL) and cooled to -78°C. $NH_{3(g)}$ was bubbled through the solution, and the reaction was stirred for 4h while warming to RT under Ar. The solution was concentrated *in vacuo* and the title compound was obtained after

25   purification (RPLC (95/5 - 5/95 H_2O/CH_3CN with 0.1% TFA, flow = 65 mL/min).

EXAMPLE 24

30   Preparation of 4-[1-hydroxy-1-(3-methyl-3H-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-benzonitrile

Step A: Preparation of 4-(3-methyl-3H-imidazole-4-carbonyl)-2-
               (naphthalen-2-yloxy)-benzonitrile

               2-Fluoro-4-[hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-
benzonitrile (as described in Example 22, Step E) (0.172 g, 0.743 mmol), 2-
5   naphthol (0.107 g, 0.743 mmol) and Cs$_2$CO$_3$ (0.727 g, 2.23 mmol) were
dissolved in anhydrous DMF (5 mL) and heated at 60°C under Ar for 2
days. The reaction was diluted with EtOAc, washed with satd. NaHCO$_3$
solution, water, and brine. The organic layer was dried (MgSO$_4$),
concentrated and purified using SiO$_2$ chromatography (1-2%
10 MeOH/CH2Cl2) to give the title compound.

Step B: Preparation of 4-[1-hydroxy-1-(3-methyl-3H-imidazol-4-yl)-
               ethyl]-2-(naphthalen-2-yloxy)-benzonitrile

               4-(3-Methyl-3H-imidazole-4-carbonyl)-2-(naphthalen-2-
15 yloxy)-benzonitrile (0.109 g, 0.308 mmol) was dissolved in anhydrous
THF (5 mL) and a 3.0 M solution of MeMgBr (0.35 mL, 1.05 mmol) was
added and stirred at RT. The reaction was quenched with NH$_4$Cl after
1h, concentrated, diluted with EtOAc, washed with satd. NaHCO$_3$
solution, water, brine, dried(MgSO$_4$) and concentrated to give the title
20 compound. FT/ICR MS (M+1) = 370.
Analysis calculated for C$_{23}$H$_{19}$N$_3$O$_2$ • 0.40 EtOAc • 0.05 H$_2$O:
               C, 72.85; H, 5.54; N, 10.36
Found: C, 72.87; H, 5.31; N, 10.29.

25   EXAMPLE 25

Preparation of 4-[1-amino-1-(3-methyl-3H-imidazol-4-yl)-ethyl]-2-
(naphthalen-2-yloxy)-benzonitrile hydrochloride

                    4-[1-Hydroxy-1-(3-methyl-3H-imidazol-4-yl)-ethyl]-2-
30 (naphthalen-2-yloxy)-benzonitrile (as described in Example 24) (0.068 g,
0.184 mmol) was dissolved in SOCl$_2$ (5 mL) and stirred at RT for 1.5h.
The solution was concentrated in vacuo and azeotroped with anhydrous

CH$_2$Cl$_2$ (3X). The solid was dissolved in CHCl$_3$ (5 mL) and cooled to -78°C. NH$_{3(g)}$ was bubbled through the solution and stirred for 4h while warming to RT under Ar. The solution was concentrated *in vacuo* and purified using reverse phase chromatography (95/5 - 5/95 H$_2$O/CH$_3$CN

5 with 0.1% TFA, flow = 65 mL/min). The compound was converted to its free base using saturated NaHCO$_3$ solution, extracted with CH$_2$Cl$_2$ (3x), dried (MgSO$_4$), filtered and treated with 1N HCl ethereal solution to give the title compound. FT/ICR MS (M+1) = 369.

10 Using the method described above, but substituting 3-{2-cyano-5-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-ethyl-*N*-phenyl-benzamide (as described in Example 26, Step C), the following compound was prepared:
3-{2-cyano-5-[1-amino-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-
15 ethyl-*N*-phenyl-benzamide.
 FT/ICR MS (M+1) = 466
Analysis calculated for C$_{28}$H$_{27}$N$_5$O$_2$ • 0.15 H$_2$O:

         C, 71.81; H, 5.88; N, 14.96;

Found: C, 71.86; H, 5.59; N, 14.78.
20

EXAMPLE 26

Preparation of 3-{2-cyano-5-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-ethyl-*N*-phenyl-benzamide
25

Step A: Preparation of 2-Fluoro-4-(3-methyl-3*H*-imidazole-4-carbonyl)-benzonitrile

         2-Fluoro-4-[hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-benzonitrile (as described in Example 22, Step E) (0.655 g, 2.83 mmol)
30 and MnO$_2$ (1.23 g, 14.2 mmol) were stirred in CH$_2$Cl$_2$ (50 mL) and CH$_3$CN (5 mL) for 72 h. The solution was filtered and concentrated to yield the title compound.

Step B: Preparation of 2-fluoro-4-[1-hydroxy-1-(3-methyl-3*H*-
               imidazol-4-yl)-ethyl]-benzonitrile

               2-Fluoro-4-(3-methyl-3*H*-imidazole-4-carbonyl)-benzonitrile

(0.603 g, 2.63 mmol) was dissolved in anhydrous THF (30 mL). A

5   solution of 3.0M MeMgBr in diethyl ether (2.55 mL, 7.65 mmol) was

added and stirred for 15 min. The reaction was quenched with NH₄Cl

solution, diluted with CH₂Cl₂ and saturated NaHCO₃ solution and

seperated. The aqueous layer was back extracted with CH₂Cl₂ (3X), the

combined organic layers dried (MgSO₄) and concentrated to give the title

10   compound.

Step C: Preparation of 3-[2-cyano-5-[1-hydroxy-1-(3-methyl-3*H*-
               imidazol-4-yl)-ethyl]-phenoxy]-*N*-ethyl-*N*-phenyl-benzamide

               2-Fluoro-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-

15   benzonitrile (0.054 g, 0.220 mmol), *N*-ethyl-3-hydroxy-*N*-phenyl-

benzamide (0.053 g, 0.220 mmol) and Cs₂CO₃ (0.143 g, 0.440 mmol) were

dissolved in anhydrous DMF (5 mL) and heated at 60°C under Ar for 4

days. The reaction was diluted with EtOAc, washed with satd. NaHCO₃

solution, water, and brine. The organic layer was dried (MgSO₄),

20   concentrated and purified using SiO₂ chromatography (1-3%

MeOH/CH₂Cl₂) to give the title compound. FAB MS (M+1) = 467

Analysis calculated for C₂₈H₂₆N₄O₂ • 0.65 H₂O:

               C, 70.31; H, 5.75; N, 11.72

Found: C, 70.31; H, 5.65; N, 11.77.

25

Using the procedures described above but substituting the requisite

phenol in Step C, the following compounds were prepared:

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(3-phenylamino-

phenoxy)-benzonitrile

30   FAB MS (M+1) = 411

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(3-phenoxy-phenoxy)-
benzonitrile

FAB MS (M+1) = 412

5   2-(3-benzoyl-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-
benzonitrile

FAB MS (M+1) = 424

2-(3-*tert*-butyl-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]

10   benzonitrile

FAB MS (M+1) = 376

2-(3-diethylamino-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-
ethyl]- benzonitrile

15   FAB MS (M+1) = 391

<u>EXAMPLE 27</u>

Preparation of 2-(5-Chloro-2-oxo-2*H*-[1,2']bipyridinyl-5'-ylmethoxy)-4-
imidazol-1-ylmethyl-benzonitrile

20

<u>Step A:</u>   <u>Preparation of 5-Chloro-5'-methyl-[1,2']bipyridinyl-2-one</u>
                    5-Chloro-2-pyridinol (2.26 g, 17.4 mmol), 2-bromo-5-
methylpyridine (3.00 g, 17.4 mmol), copper (0.022 g, 0.35 mmol) and
K$_2$CO$_3$ (2.66 g, 19.2 mmol) were heated at 180°C for 16 hrs. The brown

25   reaction mixture was cooled, diluted with EtOAc and washed with
saturated NaHCO$_3$. The aqueous layer was extracted with EtOAc (2x)
and the combined organic extracts were washed with brine, dried
(Na$_2$SO$_4$) and evaporated in vacuo. The residue was chromatographed
(silica gel, EtOAc: CH$_2$Cl$_2$ 20:80 to 50:50 gradient elution) to afford the

30   title compound as a white solid.
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.37 (s, 1H), 7.96(d, J=3.0Hz, 1H), 7.83 (d,
J=8.4Hz, 1H), 7.65(dd, J=2.4 and 8.2Hz, 1H), 7.32(dd, J=2.9 and 9.7 Hz,
1H), 6.61(d, J=9.7Hz, 1H) and 2.39(s,3H)ppm.

<u>Step B:</u>   Preparation of 5'-Bromomethyl-5-chloro-[1,2']bipyridinyl
                 -2-one

     A solution of 5-chloro-5'-methyl-[1,2']bipyridinyl-2-one (as
5   described in Step A above) (1.00 g, 4.53 mmol), N-bromosuccinimide (0.81
    g, 4.53 mmol) and AIBN (0.030 g, 0.18 mmol) in CCl$_4$ (40mL) was heated
    at reflux for 2 hrs. The solids were filtered and the filtrate collected. The
    solvent was evaporated in vacuo and the residue chromatographed
    (silica gel, EtOAc: CH$_2$Cl$_2$ 25:75 to 50:50 gradient elution) to afford the
10   title bromide.
    ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.55 (s, 1H), 8.04(d, J= 2.9 Hz, 1H), 8.01 (d,
    J=8.4Hz, 1H), 7.88 (dd, J=2.4 and 8.6Hz, 1H), 7.34(dd, J= 2.9 and 9.8Hz,
    1H), 6.61(d, J=9.9Hz, 1H) and 4.51 (s,2H) ppm.

15   <u>Step C:</u>   Preparation of 2-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-
                 ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

     Cesium carbonate (0.123 g, 0.376 mmol) was added to a
    solution of 2-hydroxy-4-imidazol-1-ylmethyl-benzonitrile (as described in
    Example 4, Step F) (0.050 g, 0.25 mmol) and 5'-bromomethyl-5-chloro-
20   [1,2']bipyridinyl-2-one (Step H) (0.079 g, 0.263 mmol) in anhydrous DMF
    (5 mL) and stirred at ambient temperature overnight. The reaction
    mixture was partitioned between EtOAc and aqueous saturated NaHCO$_3$
    solution, the organic layer separated, washed with H$_2$O, brine and dried
    (MgSO$_4$). Filtration and concentration to dryness gave the title
25   compound after chromatography (silica gel, 1-4% CH$_3$OH/CH$_2$Cl$_2$).
    FAB MS 418 (M+1).

                          <u>EXAMPLE 28</u>

30   Preparation of 4-Imidazol-1-ylmethyl-2-[2-(2-oxo-2H-pyridin-1-yl)-
    phenoxy]-benzonitrile

<u>Step A:</u>   <u>Preparation of 2-(2-oxo-2*H*-pyridin-1-yl)-anisole</u>

2-Iodoanisole (1.30 mL, 0.01 mol), 2-hydroxypyridine (0.95 g, 0.01 mol), anhydrous K_2CO_3 (2.76 g, 0.02 mol) and copper powder (0.0636 g, 0.001 mol) were combined and heated at 200°C. for 2 hr. The reaction

5   mixture was cooled, EtOAc added, and filtered. The filtrate was washed with H_2O, aqueous saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Filtration and concentration gave the title compound after chromatography (silica gel, 2% CH_3OH, CH_2Cl_2).
^{1}H NMR (CDCl3) δ 7.36 - 7.44 (m, 2H), 7.25 - 7.29 (m, 1H), 7.18 - 7.22 (m,

10   1H), 7.03 - 7.08 (m, 2H), 6.65 (d, 1H, J = 10 Hz), 6.195 (td, 1H, J = 1, 7 Hz), 3.82 (s, 3H).

<u>Step B:</u>   <u>Preparation of 2-(2-Oxo-2*H*-pyridin-1-yl)-phenol</u>

Sodium ethanethiol (0.108 g, 1.29 mmol) was added to a

15   solution of 2-(2-oxo-2*H*-pyridin-1-yl)-anisole(0.100 g, 0.497 mmol) in DMF (2 mL), and the reaction mixture was heated at 100°C. for 3 hr. The reaction mixture was partitioned between $CHCl_3$ and saturated aqueous ammonium chloride and treated with 8N HCl (pH = 1). The organic layer was separated, washed with H_2O, brine, dried (Na_2SO_4), filtered,

20   concentrated, and taken up in EtOAc, then extracted with 2% NaOH solution. The aqueous basic layer was acidified with 10% HCl solution, then extracted with EtOAc, the organic layer washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the desired product.

25   <u>Step C:</u>   Preparation of 4-Imidazol-1-ylmethyl-2-[2-(2-oxo-2*H*-
                    <u>pyridin-1-yl)-phenoxy]-benzonitrile</u>

2-Fluoro-4-imidazol-1-ylmethyl-benzonitrile (as described in Example 9, Step E) (0.0276 g, 0.137 mmol), 2-(2-oxo-2*H*-pyridin-1-yl)-phenol (0.0257 g, 0.137 mmol) and cesium carbonate (0.089 g, 0.274

30   mmol) were combined in DMF (1.2 mL) and heated at 70°C. for 18 hr. The title compound was obtained after RP HPLC on aWaters Prep Pak column eluting with a 0.1%TFA/H_2O: 0.1%TFA/CH_3CN gradient followed by conversion to the free base.
FAB MS 369 (M+1).

Analysis calculated for $C_{22}H_{16}N_4O_2 \bullet 0.3\ Et_2O$:

        C, 71.33; H, 4.90; N,14.34.

Found: C, 71.36; H, 4.83; N, 14.31.

5   Using the procedures described above , but using the appropriate iodoanisole in Step C, the following compound is prepared:

4-Imidazol-1-ylmethyl-2-[3-(2-oxo-2*H*-pyridin-1-yl)-phenoxy]-benzonitrile
FAB MS 369 (M+1).

10

<div align="center">

EXAMPLE 29

</div>

In vitro inhibition of ras farnesyl transferase

      Assays of farnesyl-protein transferase. Partially purified
15   bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL
(SEQ.ID.NO.: 12) were prepared as described by Schaber et al., J. Biol.
Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800
(1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively.
Bovine FPTase was assayed in a volume of 100 µl containing 100 mM N-
20   (2-hydroxy ethyl) piperazine-N'-(2-ethane sulfonic acid) (HEPES), pH 7.4,
5 mM MgCl2, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl
diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM
Ras-CVLS and 10 µg/ml FPTase at 31°C for 60 min. Reactions were
initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol.
25   Precipitates were collected onto filter-mats using a TomTec Mach II cell
harvestor, washed with 100% ethanol, dried and counted in an LKB β-
plate counter. The assay was linear with respect to both substrates,
FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized
during the reaction period. Purified compounds were dissolved in 100%
30   dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay.
Percentage inhibition is measured by the amount of incorporation of
radioactivity in the presence of the test compound when compared to the
amount of incorporation in the absence of the test compound.

      Human FPTase was prepared as described by Omer et al.,
35   Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed

as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 µM ZnCl$_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 µl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as

5   described above for the bovine enzyme.

The compounds of the instant invention described in the above Examples were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC$_{50}$ of <50 µM.

10

EXAMPLE 30

Modified*In vitro* GGTase inhibition asssay

The modified geranylgeranyl-protein transferase inhibition
15   assay is carried out at room temperature. A typical reaction contains (in a final volume of 50 µL): [^{3}H]geranylgeranyl diphosphate, biotinylated Ras peptide, 50 mM HEPES, pH 7.5, a modulating anion (for example 10 mM glycerophosphate or 5mM ATP), 5 mM MgCl$_2$, 10 µM ZnCl$_2$, 0.1% PEG (15-20,000), 2 mM dithiothreitol, and geranylgeranyl-
20   protein transferase type I(GGTase). The GGTase-type I enzyme employed in the assay is prepared as described in U.S. Pat. No. 5,470,832, incorporated by reference. The Ras peptide is derived from the K4B-Ras protein and has the following sequence: biotinyl-GKKKKKKKSKTKCVIM (single amino acid code) (SEQ.ID.NO.: 13).
25   Reactions are initiated by the addition of GGTase and stopped at timed intervals (typically 15 min) by the addition of 200 µL of a 3 mg/mL suspension of streptavidin SPA beads (Scintillation Proximity Assay beads, Amersham) in 0.2 M sodium phosphate, pH 4, containing 50 mM EDTA, and 0.5% BSA. The quenched reactions are allowed to stand for 2
30   hours before analysis on a Packard TopCount scintillation counter.

For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 25-fold into the enzyme assay mixture. IC$_{50}$ values are determined with Ras peptide near K_M

concentrations. Enzyme and nonsaturating substrate conditions for
inhibitor IC$_{50}$ determinations are as follows: 75 pM GGTase-I, 1.6
μM Ras peptide, 100 nM geranylgeranyl diphosphate.

5   EXAMPLE 31

Cell-based *in vitro* ras prenylation assay

                    The cell lines used in this assay consist of either Rat1 or
NIH3T3 cells transformed by either viral H-ras; an N-ras chimeric gene
10   in which the C-terminal hypervariable region of viral-H-ras was
substituted with the corresponding region from the N-ras gene; or
ras-CVLL, a viral-H-ras mutant in which the C-terminal exon encodes
leucine instead of serine, making the encoded protein a substrate for
geranylgeranylation by GGTase-I. The assay can also be performed
15   using cell lines transformed with human H-ras, N-ras or K4B-ras. The
assay is performed essentially as described in DeClue, J.E. et al.,
Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75%
confluency are treated with the test compound(s) (final concentration of
solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C,
20   the cells are labelled in 3 ml methionine-free DMEM supplemented with
10% regular DMEM, 2% fetal bovine serum, 400 μCi[35S]methionine
(1000 Ci/mmol) and test compound(s). Cells treated with lovastatin, a
compound that blocks Ras processing in cells by inhibiting the rate-
limiting step in the isoprenoid biosynthetic pathway (Hancock, J.F. et al.
25   *Cell*, 57:1167 (1989); DeClue, J.E. et al. *Cancer Res.*, 51:712 (1991);
Sinensky, M. et al. *J. Biol. Chem.*, 265:19937 (1990)), serve as a positive
control in this assay. After an additional 20 hours, the cells are lysed in
1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl$_2$/1mM
DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM
30   PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min.
Alternatively, four hours after the additon of the labelling media, the
media is removed, the cells washed, and 3 ml of media containing the
same or a different test compound added. Following an additional 16
hour incubation, the lysis is carried out as above. Aliquots of lysates
35   containing equal numbers of acid-precipitable counts are bought to 1 ml

with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti

5   rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and

10   autoradiographed. The intensities of the bands corresponding to prenylated and nonprenylated Ras proteins are compared to determine the percent inhibition of prenyl transfer to protein.

EXAMPLE 32
15

Cell-based *in vitro* anchorage independent growth assay (SALSA)

SALSA (Soft Agar-Like Surrogate Assay) measures the inhibition of anchorage-independent growth by prenyl-transferase inhibitors. Only transformed cells are able to grow anchorage-

20   independently in the SALSA format. Additionally, cells growing in the SALSA format grow in clumps, resembling the colonies formed in soft agar. SALSA may been used to measure the growth inhibition by prenyl-transferase inhibitors in a variety of transformed cell lines, including Rat1 fibroblasts transformed with viral-H-ras (H-ras/rat1), as

25   well as a panel of human tumor cell lines (HTL's).

SALSA is performed in 96-well plates that are coated with a thin film of the polymer, PolyHEMA (Poly(2-hydroxyethyl methacrylate)), which prevents cells from attaching to the plate. Rat1 fibroblast cells transformed with v-Ha-ras (this cell line has been

30   deposited in the ATCC on August 19, 1997 under the terms of the Budapest convention and has been given a designation of ATCC CRL 12387) are seeded at 5000 cells/well, grown for 4 hr, then vehicle or half-log dilutions of test compound (in either an 8 or 12 point titration) are added. The cells are then grown for 6 days at 37 degrees, without

35   changing the growth media or adding fresh compound. At day 6, cell

growth is assessed via a colorimetric assay that measures the cleavage
of the tetrazolium dye, MTT, to an insoluble purple formazan, a reaction
dependent upon mitochondrial dehydrogenases. At day 6, the cells are
incubated for 4 hr with 0.5 mg/ml MTT, and then SDS is added to 9% w/v

5   to lyse the cells and solubilize the insoluble MTT-formazan. The amount
of MTT metabolism is quantitated via spectrophotometric detection at 570
nM. Dose-inhibition curves and IC50's are determined.

EXAMPLE 33

10

Construction of SEAP reporter plasmid pDSE100

, The SEAP reporter plasmid, pDSE100 was constructed by
ligating a restriction fragment containing the SEAP coding sequence
into the plasmid pCMV-RE-AKI. The SEAP gene is derived from the

15   plasmid pSEAP2-Basic (Clontech, Palo Alto, CA). The plasmid pCMV-
RE-AKI was constructed by Deborah Jones (Merck) and contains 5
sequential copies of the 'dyad symmetry response element' cloned
upstream of a 'CAT-TATA' sequence derived from the cytomegalovirus
immediate early promoter. The plasmid also contains a bovine growth

20   hormone poly-A sequence.
The plasmid, pDSE100 was constructed as follows. A
restriction fragment encoding the SEAP coding sequence was cut out of
the plasmid pSEAP2-Basic using the restriction enzymes EcoR1 and
HpaI. The ends of the linear DNA fragments were filled in with the

25   Klenow fragment of E. coli DNA Polymerase I. The 'blunt ended' DNA
containing the SEAP gene was isolated by electrophoresing the digest in
an agarose gel and cutting out the 1694 base pair fragment. The vector
plasmid pCMV-RE-AKI was linearized with the restriction enzyme Bgl-
II and the ends filled in with Klenow DNA Polymerase I. The SEAP

30   DNA fragment was blunt end ligated into the pCMV-RE-AKI vector and
the ligation products were transformed into DH5-alpha E. coli cells
(Gibco-BRL). Transformants were screened for the proper insert and
then mapped for restriction fragment orientation. Properly oriented
recombinant constructs were sequenced across the cloning junctions to

35   verify the correct sequence. The resulting plasmid contains the SEAP

coding sequence downstream of the DSE and CAT-TATA promoter elements and upstream of the BGH poly-A sequence.

Cloning of a Myristylated viral-H-*ras* expression plasmid

5

A DNA fragment containing viral-H-*ras* can be PCRed from plasmid "H-1" (Ellis R. et al. J. Virol. **36**, 408, 1980) using the following oligos.

Sense strand:

10 5'TCTCCTCGAGGCCACCATGGGGAGTAGCAAGAGCAAGCCTAA GGACCCCAGCCAGCGCCGGATGACAGAATACAAGCTTGTGGTG G 3'. (SEQ.ID.NO.: 14)

Antisense: 5'CACATCTAGATCAGGACAGCACAGACTTGCAGC 3'.
15 (SEQ.ID.NO.: 15)

A sequence encoding the first 15 aminoacids of the v-src gene, containing a myristylation site, is incorporated into the sense strand oligo. The sense strand oligo also optimizes the 'Kozak' translation
20 initiation sequence immediately 5' to the ATG start site.To prevent prenylation at the viral-*ras* C-terminus, cysteine 186 would be mutated to a serine by substituting a G residue for a C residue in the C-terminal antisense oligo. The PCR primer oligos introduce an XhoI site at the 5' end and a XbaI site at the 3'end. The XhoI-XbaI fragment can be ligated
25 into the mammalian expression plasmid pCI (Promega) cut with XhoI and XbaI. This results in a plasmid in which the recombinant myr- viral-H-ras gene is constitutively transcribed from the CMV promoter of the pCI vector.

30 Cloning of a viral-H-*ras*-CVLL expression plasmid

A viral-H-*ras* clone with a C-terminal sequence encoding the amino acids CVLL can be cloned from the plasmid "H-1" (Ellis R. et al. J. Virol. **36**, 408, 1980) by PCR using the following oligos.
35

Sense strand:
5'TCTCCTCGAGGCCACCATGACAGAATACAAGCTTGTGGTGG-3'
(SEQ.ID.NO.: 16)

5   Antisense strand:
5'CACTCTAGACTGGTGTCAGAGCAGCACACACTTGCAGC-3'
(SEQ.ID.NO.: 17)

The sense strand oligo optimizes the 'Kozak' sequence and adds an XhoI
10   site. The antisense strand mutates serine 189 to leucine and adds an
XbaI site. The PCR fragment can be trimmed with XhoI and XbaI and
ligated into the XhoI-XbaI cut vector pCI (Promega). This results in a
plasmid in which the mutated viral-H-*ras*-CVLL gene is constitutively
transcribed from the CMV promoter of the pCI vector.
15

Cloning of c-H-*ras*-Leu61 expression plasmid
The human c-H-*ras* gene can be PCRed from a human cerebral cortex
cDNA library (Clontech) using the following oligonucleotide primers.

20   Sense strand:
5'-GAGAGAATTCGCCACCATGACGGAATATAAGCTGGTGG-3'
(SEQ.ID.NO.: 18)

Antisense strand:
25   5'-GAGAGTCGACGCGTCAGGAGAGCACACACTTGC-3'
(SEQ.ID.NO.: 19)

The primers will amplify a c-H-*ras* encoding DNA fragment with the
primers contributing an optimized 'Kozak' translation start sequence,
30   an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end.
After trimming the ends of the PCR product with EcoRI and Sal I, the c-
H-ras fragment can be ligated ligated into an EcoRI -Sal I cut
mutagenesis vector pAlter-1 (Promega). Mutation of glutamine-61 to a
leucine can be accomplished using the manufacturer's protocols and
35   the following oligonucleotide:

-139-

5'-CCGCCGGCCTGGAGGAGTACAG-3' (SEQ.ID.NO.: 20)

After selection and sequencing for the correct nucleotide substitution,
the mutated c-H-*ras*-Leu61 can be excised from the pAlter-1 vector,
using EcoRI and Sal I, and be directly ligated into the vector pCI
(Promega) which has been digested with EcoRI and Sal I. The new
recombinant plasmid will constitutively transcribe c-H-*ras*-Leu61 from
the CMV promoter of the pCI vector.

Cloning of a c-N-*ras*-Val-12 expression plasmid

The human c-N-*ras* gene can be PCRed from a human cerebral cortex
cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGAATTCGCCACCATGACTGAGTACAAACTGGTGG-3'
(SEQ.ID.NO.: 21)

Antisense strand:
5'-GAGAGTCGACTTGTTACATCACCACACATGGC-3' (SEQ.ID.NO.:
22)

The primers will amplify a c-N-*ras* encoding DNA fragment with the
primers contributing an optimized 'Kozak' translation start sequence,
an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end.
After trimming the ends of the PCR product with EcoRI and Sal I, the c-
N-ras fragment can be ligated into an EcoRI -Sal I cut mutagenesis
vector pAlter-1 (Promega). Mutation of glycine-12 to a valine can be
accomplished using the manufacturer's protocols and the following
oligonucleotide:

5'-GTTGGAGCAGTTGGTGTTGGG-3' (SEQ.ID.NO.: 23)

After selection and sequencing for the correct nucleotide substitution, the mutated c-N-*ras*-Val-12 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with EcoRI and Sal I. The new
5   recombinant plasmid will constitutively transcribe c-N-*ras*-Val-12 from the CMV promoter of the pCI vector.

Cloning of a c-K-*ras*-Val-12 expression plasmid

10   The human c-K-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGGTACCGCCACCATGACTGAATATAAACTTGTGG-3'
15   (SEQ.ID.NO.: 24)

Antisense strand:
5'-CTCTGTCGACGTATTTACATAATTACACACTTTGTC-3'
(SEQ.ID.NO.: 25)
20

The primers will amplify a c-K-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, a KpnI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with Kpn I and Sal I, the
25   c-K-*ras* fragment can be ligated into a KpnI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of cysteine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

30   5'-GTAGTTGGAGCTGTTGGCGTAGGC-3' (SEQ.ID.NO.: 26)

After selection and sequencing for the correct nucleotide substitution, the mutated c-K-*ras*-Val-12 can be excised from the pAlter-1 vector, using KpnI and Sal I, and be directly ligated into the vector pCI
35   (Promega) which has been digested with KpnI and Sal I. The new

recombinant plasmid will constitutively transcribe c-K-*ras*-Val-12 from the CMV promoter of the pCI vector.

SEAP assay

5   Human C33A cells (human epitheial carcenoma - ATTC collection) are seeded in 10cm tissue culture plates in DMEM + 10% fetal calf serum + 1X Pen/Strep + 1X glutamine + 1X NEAA. Cells are grown at 37°C in a 5% CO_2 atmosphere until they reach 50 -80% of conflunecy.

10   The transient transfection is performed by the $CaPO_4$ method (Sambrook et al., 1989). Thus, expression plasmids for H-*ras*, N-*ras*, K-*ras*, Myr-*ras* or H-*ras*-CVLL are co-precipitated with the DSE-SEAP reporter construct. For 10cm plates 600μl of $CaCl_2$ -DNA solution is added dropwise while vortexing to 600μl of 2X HBS buffer to give 1.2ml

15   of precipitate solution (see recipes below). This is allowed to sit at room temperature for 20 to 30 minutes. While the precipitate is forming, the media on the C33A cells is replaced with DMEM (minus phenol red; Gibco cat. # 31053-028)+ 0.5% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and nonessential aminoacids). The $CaPO_4$-DNA

20   precipitate is added dropwise to the cells and the plate rocked gently to distribute. DNA uptake is allowed to proceed for 5-6 hrs at 37°C under a 5% CO_2 atmosphere.

Following the DNA incubation period, the cells are washed with PBS and trypsinized with 1ml of 0.05% trypsin. The 1 ml of

25   trypsinized cells is diluted into 10ml of phenol red free DMEM + 0.2% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and NEAA). Transfected cells are plated in a 96 well microtiter plate (100μl/well) to which drug, diluted in media, has already been added in a volume of 100μl. The final volume per well is 200μl with each drug concentration

30   repeated in triplicate over a range of half-log steps.

Incubation of cells and drugs is for 36 hrs at 37° under CO_2. At the end of the incubation period, cells are examined microscopically for evidence of cell distress. Next, 100μl of media containing the secreted alkaline phosphatase is removed from each well and transferred to a

35   microtube array for heat treatment at 65°C for 1 hr to inactivate

endogenous alkaline phosphatases (but not the heat stable secreted phosphatase).

The heat treated media is assayed for alkaline phosphatase by a luminescence assay using the luminescence reagent CSPD®

5   (Tropix, Bedford, Mass.). A volume of 50 μl media is combinRased with 200 μl of CSPD cocktail and incubated for 60 minutes at room temperature.   Luminesence is monitored using an ML2200 microplate luminometer (Dynatech). Luminescence reflects the level of activation of the fos reporter construct stimulated by the transiently expressed

10 protein.

<u>DNA-CaPO$_4$ precipitate for 10cm. plate of cells</u>

    Ras expression plasmid (1μg/μl)   10μl

15 DSE-SEAP Plasmid (1μg/μl)   2μl

    Sheared Calf Thymus DNA (1μg/μl) 8μl

    2M CaCl$_2$ 74μl

    dH$_2$O   506μl

20 <u>2X HBS Buffer</u>

    280mM NaCl

    10mM KCl

    1.5mM Na$_2$HPO$_4$ 2H$_2$O

25 12mM dextrose

    50mM HEPES

    Final pH = 7.05

    <u>Luminesence Buffer (26ml)</u>

30 Assay Buffer   20ml

    Emerald Reagent™ (Tropix) 2.5ml

    100mM homoarginine 2.5ml

    CSPD Reagent® (Tropix)1.0ml

35 Assay Buffer

Add 0.05M Na_2CO_3 to 0.05M $NaHCO_3$ to obtain pH 9.5. Make 1mM in $MgCl_2$

EXAMPLE 34

5 *In vivo tumor growth inhibition assay (nude mouse)*

      In vivo efficacy as an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art. Examples of such *in vivo* efficacy studies are described by N. E. Kohl et al. (*Nature Medicine*, 1:792-797 (1995)) and N. E. Kohl et al. (*Proc. Nat. Acad. Sci.*

10 *U.S.A.*, 91:9141-9145 (1994)).

      Rodent fibroblasts transformed with oncogenically mutated human Ha-*ras* or Ki-*ras* (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly

15 assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously starting on day 1 and daily for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a

20 total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

WHAT IS CLAIMED IS:

1.   A compound of formula A:

A

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

    a)   hydrogen,

    b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from: -

    a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

    f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

      h) N_3,

      i) $R^9S(O)_q$,

      j) $R^8HC=CH$-,

      k) $R^8C\equiv C$-, and

5   l) OR^8;

R^3, R^4 and R^5 are independently selected from:

      H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl,

      N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl,

10   unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-,

      C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8,

      -$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

$$-\overset{\displaystyle |}{\underset{\displaystyle OH}{C}}=\overset{\displaystyle}{\underset{\displaystyle H}{C}}-R^8$$

      -$(C_1$-C_6 alkyl)$C(O)R^8$, -$CH=CH$-R^8 and   ;

15 R^6 is independently selected from:

      a)   hydrogen,

      b)   CN,

      c) NO_2,

      d)   halogen,

20   e)   aryl, unsubstituted or substituted,

      f)   heteroaryl, unsubstituted or substituted,

      g) C_1-C_6 alkyl, unsubstituted or substituted,

      h) R^8O-,

      i) N_3,

25   j) $R^9S(O)_q$-,

      k)   -$HC=CH_2$,

      l)   -$C\equiv CH$,

      m) CF_3

      n) $R^8O(C=O)$-, and

30   o) $R^8(O=C)O$-;

   R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

5   H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and

unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted

10   or substituted aryl, unsubstituted or substituted heterocycle,
-$(C_1$-C_6 alkyl)OR^8, -$(C_1$-C_6 alkyl)$OC(O)(C_1$-C_6 alkyl), -$(C_1$-C_6
alkyl)$N(R^8)_2$, and -$(C_1$-C_6 alkyl)$NHC(O)(C_1$-C_6 alkyl)R^8;

A^1, A^2 and A^3 are independently selected from:

15   a)   a bond,

          b)   -HC=CH-,

          c)   -C≡C-,

          d)   -O-,

          e)   -(C=O)-,

20   f)   -O(C=O)-,

          g)   -(C=O)O-,

          h)   -NR^8-,

          i)   -$C(O)N(R^8)$-,

          j)   -$N(R^8)C(O)$-,

25   k)   -NHC(O)NH-,

          l)   -$S(O)_q$-,

          m)   -$S(O)_qNH$-, and

          n)   -$NHS(O)_q$-;

30   A^4 is selected from a bond, $C(O)$, $C=CH_2$, or spiro C_3-C_6 cycloalkyl;

W is selected from:

          a)   hydrogen,

          b)   heterocycle, and

      c)   aryl;

X is selected from:
      a)   aryl,
      b)   cycloalkyl,
      c)   heterocycle, and
      d)   a bond;

Y is selected from:
      a)   aryl, unsubstituted or substituted
      b)   heterocycle, unsubstituted or substituted, and
      c)   cycloalkyl;

m is $0, 1, 2, 3$ or 4;
n is $0, 1, 2, 3$ or 4;
p is $0, 1, 2, 3$ or 4;
q is $0, 1$ or 2;
r is $0, 1, 2$ or 3;
s is $0, 1, 2, 3$ or 4; and;
t is $0, 1, 2$ or 3;

provided that

$$-\xi-A^{1}(C(R^{1a})_{2})_{n}A^{2}(C(R^{1a})_{2})_{\overline{n}} \overset{\displaystyle \left(\!\!R^{6}\!\!\right)_{t}}{\underset{\displaystyle |}{X}} -(C(R^{1b})_{2})_{p}A^{3}(C(R^{1b})_{2})_{\overline{p}}\xi\cdot$$
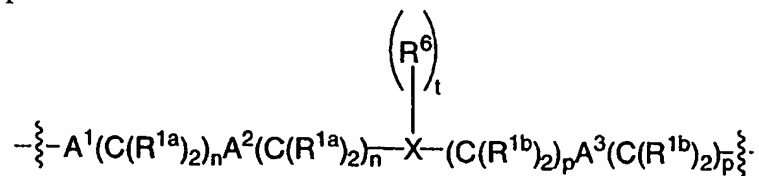
is not a bond;

or the pharmaceutically acceptable salts thereof.

    2.   The compound of Claim 1, illustrated by formula A:

$$(R^{13})_s$$
$$|$$
$$W$$
$$\backslash$$
$$A^4$$
$$|$$
$$(C(R^{1c})_2)_m$$

$$\left(R^3\right)_r \underset{R^2}{\overset{|}{\bigcirc}} - A^1(C(R^{1a})_2)_n A^2(C(R^{1a})_2)_{\overline{n}} \overset{(R^6)_t}{\overset{|}{X}} - (C(R^{1b})_2)_p A^3 (C(R^{1b})_2)_{\overline{p}} - Y \overset{R^5}{\underset{R^4}{<}}$$

A

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

5   a)   hydrogen,

       b)   unsubstituted or substituted aryl, unsubstituted or
               substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl,
               C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-,
               $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

10   c) C_1-C_6 alkyl, unsubstituted or substituted by aryl,
               heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6
               alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or
               $R^8C(O)O$-;

15 R^2 is selected from:

       a)   hydrogen,

       b)   CN,

       c) NO_2,

       d)   halogen,

20   e)   aryl, unsubstituted or substituted

       f)   heteroaryl, unsubstituted or substituted

       g) C_1-C_6 alkyl, unsubstituted or substituted

       h) N_3,

       i) $R^9S(O)_q$,

25   j) $R^8HC=C$-,

    k) $R^8 C \equiv C$-, and

    l) OR^8;

R^3, R^4 and R^5 are independently selected from:

    H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl,
N_3, $R^9 S(O)_q$, -$C \equiv CH$, unsubstituted or substituted aryl,
unsubstituted or substituted heterocycle, CF_3, CF_3O-, $CF_3 CH_2 O$-,
C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8,
-$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

$$-\underset{\underset{OH}{|}}{C}=\underset{H}{C}-R^8$$

-$(C_1$-C_6 alkyl)$C(O)R^8$, -$CH=CH$-R^8 and   ;

R^6 is independently selected from:

    a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted,

    f)   heteroaryl, unsubstituted or substituted,

    g) C_1-C_6 alkyl, unsubstituted or substituted,

    h) $R^8 O$-, unsubstituted or substituted,

    i) N_3,

    j) $R^9 S(O)_q$-,

    k)   -$HC=CH_2$,

    l)   -$C \equiv CH$,

    m) CF_3

    n) $R^8 O(C=O)$-, and

    o) $R^8 (O=C)O$-;

R^8 is independently selected from

    hydrogen, unsubstituted or substituted C_1-C_6 alkyl,
    cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and
unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted
or substituted aryl, unsubstituted or substituted heterocycle,
-(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)$OC(O)$(C_1-C_6 alkyl), -(C_1-C_6
alkyl)$N(R^8)_2$, and -(C_1-C_6 alkyl)$NHC(O)$(C_1-C_6 alkyl)R^8;

A^1, A^2 and A^3 are independently selected from:

a)	a bond,
b)	-HC=CH-,
c)	-C≡C-,
d)	-O-,
e)	-(C=O)-,
f)	-O(C=O)-,
g)	-(C=O)O-,
h)	-NR^8-,
i)	-$C(O)N(R^8)$-,
j)	-$N(R^8)C(O)$-,
k)	-NHC(O)NH-,
l)	-$S(O)_q$-,
m)	-$S(O)_q$NH-, and
n)	-$NHS(O)_q$-;

A^4 is selected from a bond, C(O), C=CH_2, or spiro C_3-C_6 cycloalkyl;

W is selected from:

a)	heterocycle, and
b)	aryl;

X is selected from:

a)	aryl,
b)	cycloalkyl,

      c)   heterocycle, and

      d)   a bond;

Y is selected from:

5   a)   aryl,

      b)   heterocycle, and

      c)   cycloalkyl;

m is 0, 1, 2, 3 or 4;

10   n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 0, 1 or 2;

r is 1 or 2;

s is 0, 1, 2, 3 or 4; and

15   t is   0, 1, 2 or 3;

provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_{\overline{n}}\overset{\displaystyle\left(\!\!\overset{\displaystyle R^6}{\underset{\displaystyle|}{}}\!\!\right)_t}{X}-(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_{\overline{p}}\xi-$$

is not a bond;

20

or the pharmaceutically acceptable salts thereof.

     3.   The compound of Claim 1, illustrated by formula B:

$$(R^{13})_s$$
$$W$$
$$A^4$$
$$(C(R^{1c})_2)_m$$

$$R^3 - \overset{\underset{\displaystyle R^2}{}}{\bigcirc} - A^1(C(R^{1a})_2)_n A^2(C(R^{1a})_2)_{\bar{n}} - X - (C(R^{1b})_2)_p A^3(C(R^{1b})_2)_{\bar{p}} - \overset{R^5}{\bigcirc}_{R^4}$$

$$(R^6)_t$$

B

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

     a)   hydrogen,

     b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

     c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

     a)   hydrogen,

     b)   CN,

     c) NO_2,

     d)   halogen,

     e)   aryl, unsubstituted or substituted

     f)   heteroaryl, unsubstituted or substituted

     g) C_1-C_6 alkyl, unsubstituted or substituted

     h) N_3,

     i) $R^9S(O)_q$,

     j) $R^8HC=CH$-,

     k) $R^8C\equiv C$-, and

l) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8, -$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

$$-\overset{\underset{OH}{|}}{C}=\overset{\underset{H}{}}{C}-R^8$$

-$(C_1$-C_6 alkyl)$C(O)R^8$, -$CH=CH$-R^8 and ;

R^6 is independently selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O-,

i) N_3,

j) $R^9S(O)_q$-,

k)   -$HC=CH_2$,

l)   -$C\equiv CH$,

m) CF_3

n) $R^8O(C=O)$-, and

o) R^8 $(O=C)O$-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl, cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, -(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)$OC(O)$(C_1-C_6 alkyl), -(C_1-C_6 alkyl)$N(R^8)_2$, and -(C_1-C_6 alkyl)$NHC(O)$(C_1-C_6 alkyl)R^8;

A^1, A^2 and A^3 are independently selected from:

a) a bond,
b) -HC=CH-,
c) -C≡C-,
d) -O-,
e) -(C=O)-,
f) -O(C=O)-,
g) -(C=O)O-,
h) -NR^8-,
i) -$C(O)N(R^8)$-,
j) -$N(R^8)C(O)$-,
k) -NHC(O)NH-,
l) -$S(O)_q$-,
m) -$S(O)_qNH$-, and
n) -$NHS(O)_q$-;

A^4 is selected from a bond, C(O), C=CH_2, or spiro C_3-C_6 cycloalkyl;

W is selected from:

a) heterocycle, and
b) aryl;

X is selected from:

a) aryl,
b) cycloalkyl,

- 155 -

      c)   heterocycle, and

      d)   a bond;

m is 0, 1, 2, 3 or 4;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

q is   0, 1 or 2;

s is   0, 1, 2, 3 or 4; and

t is   0, 1, 2, or 3;

provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n\!-\!X\!-\!(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_p\xi-$$

$$\left(R^6\right)_t$$

is not a bond;

or the pharmaceutically acceptable salts thereof.

    4.   The compound of Claim 3, illustrated by formula B:

B

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

      a)   hydrogen,

b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

    a)   hydrogen,
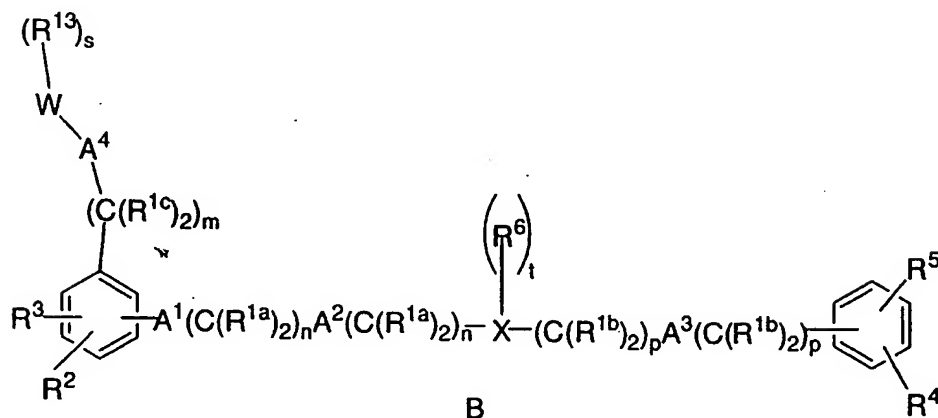
    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

    f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

    h) N_3,

    i) $R^9S(O)_q$,

    j) $R^8HC=CH$-,

    k) $R^8C\equiv C$, and

    l) OR^8;

R^3, R^4 and R^5 are independently selected from:

    H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, $-C(O)R^8$, $-O(C_1$-C_6 alkyl)OR^8, $-NHC(O)R^8$, aralkyl, heteroaralkyl, $-(C_1$-C_6 alkyl)OR^8,

$$-\underset{\underset{OH}{|}}{C}=\underset{H}{C}-R^8$$

    $-(C_1$-C_6 alkyl)$C(O)R^8$, $-CH=CH$-R^8 and;

R^6 is independently selected from:

    a)   hydrogen,

b)   CN,

c)   NO$_2$,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g)   C$_1$-C$_6$ alkyl, unsubstituted or substituted,

h)   R^{8}O-,

i)   N$_3$,

j)   R^{9}S(O)$_q$-,

k)   -HC=CH$_2$,

l)   -C≡CH,

m)   CF$_3$

n)   R^{8}O(C=O)-, and

o)   R^8 (O=C)O-;

R^8 is independently selected from

       hydrogen, unsubstituted or substituted C$_1$-C$_6$ alkyl,

       cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

       H, unsubstituted or substituted C$_1$-C$_6$ alkyl, benzyl and

       unsubstituted or substituted aryl;

R^{13} is independently selected from

       H, unsubstituted or substituted C$_1$-C$_6$ alkyl, unsubstituted

       or substituted aryl, unsubstituted or substituted heterocycle,

       -(C$_1$-C$_6$ alkyl)OR^8, -(C$_1$-C$_6$ alkyl)OC(O)(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$

       alkyl)N(R^8)$_2$, and -(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8;

A^1 is selected from:

a)   a bond,

b)   -O-,

c)   -(C=O)-,

d)   -NR^8-,

e)   -C(O)N(R^8)-, and

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f)   -S(O)$_q$-;

A^2 and A^3 are independently selected from:

   a)   a bond,
5 b)   -HC=CH-,
   c)   -C≡C-,
   d)   -O-,
   e)   -(C=O)-,
   f)   -O(C=O)-,
10 g)   -(C=O)O-,
   h)   -NR^8-,
   i)   -C(O)N(R^8)-,
   j)   -N(R^8)C(O)-,
   k)   -NHC(O)NH-,
15 l)   -S(O)$_q$-,
   m)   -S(O)$_q$NH-, and
   n)   -NHS(O)$_q$-;

A^4 is selected from a bond, C(O), C=CH$_2$, or spiro C$_3$-C$_6$ cycloalkyl;
20

W is a heterocycle,

X is selected from:
   a)   aryl,
25 b)   heterocycle, and
   c)   a bond;
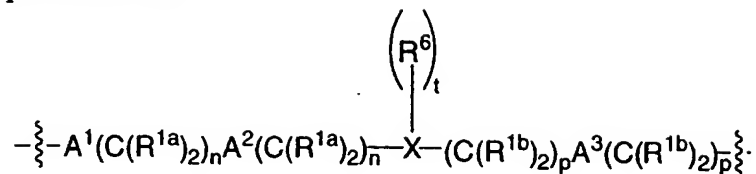
   m is 0, 1, 2, 3 or 4;
   n is 0, 1, 2, 3 or 4;
30 p is 0, 1, 2, 3 or 4;
   q is 0, 1 or 2;
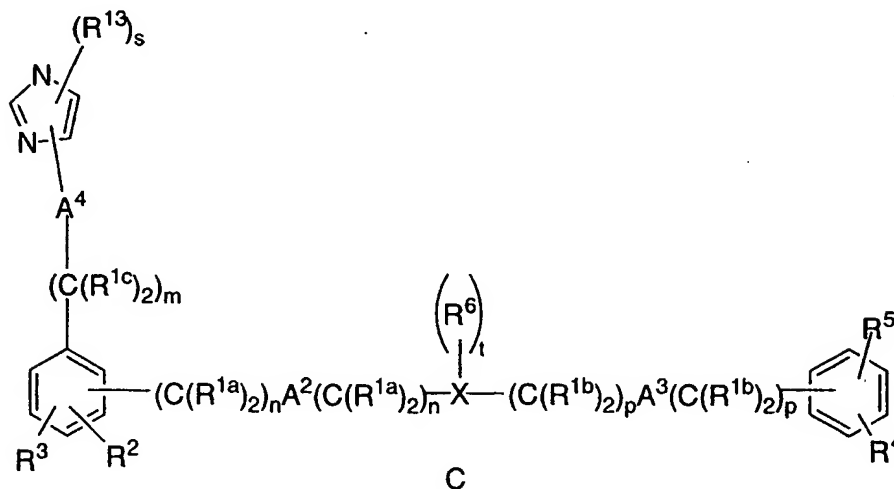   s is 0, 1, 2, 3 or 4; and
   t is 0, 1, 2 or 3;

provided that

$$-\text{-}A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_{\overline{n}}X\text{-}(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_{\overline{p}}\text{-}$$

(with $(R^6)_t$ substituent on X)

is not a bond;

5   or the pharmaceutically acceptable salts thereof.

      5.   The compound of Claim 1, illustrated by formula C:

C

wherein:

10   R^{1a}, R^{1b} and R^{1c} are independently selected from:

      a)   hydrogen,

      b)   unsubstituted or substituted aryl, unsubstituted or
              substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl,
              C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-,

15            $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

      c) C_1-C_6 alkyl, unsubstituted or substituted by aryl,
              heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6
              alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or
              $R^8C(O)O$-;

R^2 is selected from:

    a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted

    f)   heteroaryl, unsubstituted or substituted

    g) C_1-C_6 alkyl, unsubstituted or substituted

    h) $R^9S(O)_q$, and

    i) OR^8;

R^3, R^4 and R^5 are independently selected from:

    H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, HC≡C-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -C(O)R^8, -O(C_1-C_6 alkyl)OR^8, -NHC(O)R^8, aralkyl, heteroaralkyl, -(C_1-C_6 alkyl)OR^8,

$$-\overset{}{\underset{OH}{C}}=\overset{H}{C}-R^8$$

    -(C_1-C_6 alkyl)C(O)R^8, -CH=CH-R^8 and   ;

R^6 is independently selected from:

    a)   hydrogen,

    b)   CN,

    c) NO_2,

    d)   halogen,

    e)   aryl, unsubstituted or substituted,

    f)   heteroaryl, unsubstituted or substituted,

    g) C_1-C_6 alkyl, unsubstituted or substituted,

    h) R^8O-,

    i) N_3,

    j) $R^9S(O)_q$-,

    k) CF_3

    l) $R^8O(C=O)$-, and

m)　　R^8(O=C)O-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C$_1$-C$_6$ alkyl,

cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C$_1$-C$_6$ alkyl, benzyl and

unsubstituted or substituted aryl;

R^{13} is independently selected from

H, unsubstituted or substituted C$_1$-C$_6$ alkyl, unsubstituted

or substituted aryl, unsubstituted or substituted heterocycle,

-(C$_1$-C$_6$ alkyl)OR^8, -(C$_1$-C$_6$ alkyl)OC(O)(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$

alkyl)N(R^8)$_2$, and -(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8;

A^2 is selected from:

a)　　a bond,

b)　　-HC=CH-,

c)　　-C≡C-,

d)　　-O-,

e)　　-(C=O)-,

f)　　-O(C=O)-,

g)　　-(C=O)O-,

h)　　-NR^8-,

i)　　-C(O)N(R^8)-,

j)　　-N(R^8)C(O)-,

k)　　-NHC(O)NH-,

l)　　-S(O)$_q$-,

m)　　-S(O)$_q$NH-, and

n)　　-NHS(O)$_q$-;

A^3 is selected from:

a)　　a bond,

b)   -O-,

c) $-S(O)_q-$,

d) $-S(O)_qNH-$,

e) $-NR^8-$,

f) $-(C=O)-$,

g) $-(C=O)O-$,

h) $-O(C=O)-$,

i) $-C(O)N(R^8)-$,

j) $-N(R^8)C(O)-$, and

k)   -NHC(O)NH-;

A^4 is selected from a bond, C(O), $C=CH_2$, or spiro C_3-C_6 cycloalkyl;

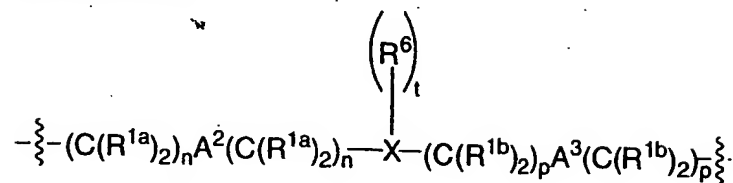X is selected from:

a)   aryl,

b)   heterocycle, and

c)   a bond;

m is   0, 1, 2, 3 or 4;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

q is   0, 1 or 2;

s is   0, 1, 2, 3 or 4; and

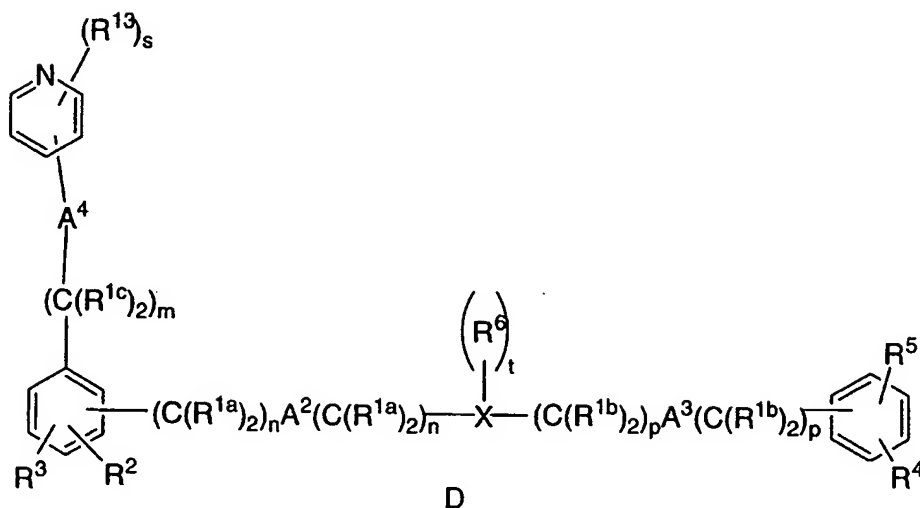t is   0, 1, 2 or 3;

provided that

$$-\xi-(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n-X-(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_p-\xi-$$

with $(R^6)_t$

is not a bond;

or the pharmaceutically acceptable salts thereof.

6.   The compound of Claim 1, illustrated by formula D:

D

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

5   a)   hydrogen,

     b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

10   c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

15   R^2 is selected from:

     a)   hydrogen,

     b)   CN,

     c) NO_2,

     d)   halogen,

20   e)   aryl, unsubstituted or substituted

     f)   heteroaryl, unsubstituted or substituted

     g) C_1-C_6 alkyl, unsubstituted or substituted

h) $R^9S(O)_q$, and

i) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO_2, halogen, unsubstituted or substituted C_1-C_6 alkyl, N_3, $R^9S(O)_q$, $HC\equiv C$-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF_3, CF_3O-, CF_3CH_2O-, C_3-C_{10} cycloalkyl, OR^8, $N(R^8)_2$, -$C(O)R^8$, -$O(C_1$-C_6 alkyl)OR^8, -$NHC(O)R^8$, aralkyl, heteroaralkyl, -$(C_1$-C_6 alkyl)OR^8,

$$-\overset{\displaystyle}{\underset{\displaystyle OH}{C}}=\overset{\displaystyle}{\underset{\displaystyle H}{C}}-R^8$$

-$(C_1$-C_6 alkyl)$C(O)R^8$, -$CH=CH$-R^8 and ;

R^6 is independently selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O-,

i) N_3,

j) $R^9S(O)_q$-,

k) CF_3

l) $R^8O(C=O)$-, and

m) R^8 $(O=C)O$-;

R^8 is independently selected from

hydrogen, unsubstituted or substituted C_1-C_6 alkyl, cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from

H, unsubstituted or substituted C_1-C_6 alkyl, benzyl and unsubstituted or substituted aryl;

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R^{13} is independently selected from

        H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted

        or substituted aryl, unsubstituted or substituted heterocycle,

        -(C_1-C_6 alkyl)OR^8, -(C_1-C_6 alkyl)OC(O)(C_1-C_6 alkyl), -(C_1-C_6

        alkyl)$N(R^8)_2$, and -(C_1-C_6 alkyl)NHC(O)(C_1-C_6 alkyl)R^8;

A^2 is selected from:

    a)   a bond,

    b)   -HC=CH-,

    c)   -C≡C-,

    d)   -O-,

    e)   -(C=O)-,

    f)   -O(C=O)-,

    g)   -(C=O)O-,

    h)   -NR^8-,

    i)   -C(O)$N(R^8)$-,

    j)   -$N(R^8)$C(O)-,

    k)   -NHC(O)NH-,

    l)   -$S(O)_q$-,

    m)   -$S(O)_q$NH-, and

    n)   -$NHS(O)_q$-;

A^3 is selected from:

    a)   a bond,

    b)   -O-,

    c)   -$S(O)_q$-,

    d)   -$S(O)_q$NH-,

    e)   -NR^8-,

    f)   -(C=O)-,

    g)   -(C=O)O-,

    h)   -O(C=O)-,

    i)   -C(O)$N(R^8)$-,

    j)   -$N(R^8)$C(O)-, and

    k)   -NHC(O)NH-;

A^4 is selected from a bond, $C(O)$, $C=CH_2$, or spiro C_3-C_6 cycloalkyl;

X is selected from:
5   a)   aryl,
           b)   heterocycle, and
           c)   a bond;

m is   0, 1, 2, 3 or 4;
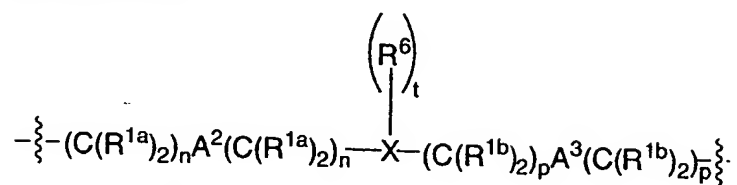10   n is   0, 1, 2, 3 or 4;
p is   0, 1, 2, 3 or 4;
q is   0, 1 or 2; and
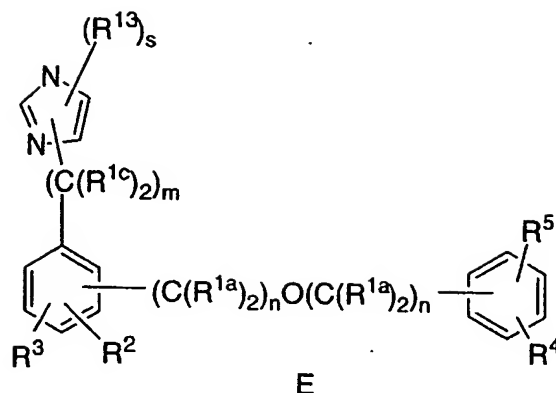s is   0, 1, 2, 3 or 4; and
t is   0, 1, 2, or 3;
15

provided that

$$-\xi-(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_{\bar{n}}-X\overset{\left(\underset{}{R^6}\right)_t}{\rule{0.3pt}{18pt}}-(C(R^{1b})_2)_pA^3(C(R^{1b})_2)_{\bar{p}}\xi \cdot$$

is not a bond;

20   or the pharmaceutically acceptable salts thereof.

7.   The compound of Claim 1, illustrated by formula E:

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E

wherein:

R^{1a} and R^{1c} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

a) hydrogen,

b) CN,

c) NO_2,

d) halogen,

e) aryl, unsubstituted or substituted

f) heteroaryl, unsubstituted or substituted

g) C_1-C_6 alkyl, unsubstituted or substituted

h) $R^9S(O)_q$, and

i) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO$_2$, halogen, unsubstituted or substituted C$_1$-C$_6$ alkyl, N$_3$, R^{9}S(O)$_q$, HC≡C-, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, CF$_3$, CF$_3$O-, CF$_3$CH$_2$O-, C$_3$-C$_{10}$ cycloalkyl, OR^8, N(R^8)$_2$, -C(O)R^8, -O(C$_1$-C$_6$ alkyl)OR^8, -NHC(O)R^8, aralkyl, heteroaralkyl, -(C$_1$-C$_6$ alkyl)OR^8,

$$-\overset{}{\underset{\underset{OH}{|}}{C}}=\overset{}{\underset{H}{C}}-R^8$$

-(C$_1$-C$_6$ alkyl)C(O)R^8, -CH=CH-R^8 and ;

R^8 is independently selected from
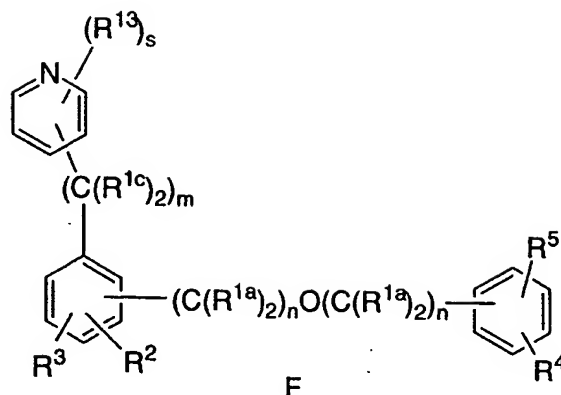hydrogen, unsubstituted or substituted C$_1$-C$_6$ alkyl, cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from
H, unsubstituted or substituted C$_1$-C$_6$ alkyl, benzyl and unsubstituted or substituted aryl;

R^{13} is independently selected from
H, unsubstituted or substituted C$_1$-C$_6$ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, -(C$_1$-C$_6$ alkyl)OR^8, -(C$_1$-C$_6$ alkyl)OC(O)(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$ alkyl)N(R^8)$_2$, and -(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8;

m is   0, 1, 2, 3 or 4;
n is   0, 1, 2, 3 or 4;
q is   0, 1 or 2; and
s is   0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

8.   The compound of Claim 1, illustrated by formula F:

F

wherein:

R^{1a} and R^{1c} are independently selected from:

a)   hydrogen,

b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, $R^8(C_1$-C_6 alkyl)O-, N_3, $N(R^8)_2$ or -OC(O)O-heteroaralkyl;

c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

R^2 is selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted

f)   heteroaryl, unsubstituted or substituted

g) C_1-C_6 alkyl, unsubstituted or substituted

h) $R^9S(O)_q$, and

i) OR^8;

R^3, R^4 and R^5 are independently selected from:

H, CN, NO$_2$, halogen, unsubstituted or substituted C$_1$-C$_6$ alkyl,
N$_3$, R^{9}S(O)$_q$, HC≡C-, unsubstituted or substituted aryl,
unsubstituted or substituted heterocycle, CF$_3$, CF$_3$O-, CF$_3$CH$_2$O-,
C$_3$-C$_{10}$ cycloalkyl, OR^8, N(R^8)$_2$, -C(O)R^8, -O(C$_1$-C$_6$ alkyl)OR^8,
-NHC(O)R^8, aralkyl, heteroaralkyl, -(C$_1$-C$_6$ alkyl)OR^8,

$$-\underset{\underset{OH}{\vert}}{C}=\underset{\underset{H}{\vert}}{C}-R^8$$

-(C$_1$-C$_6$ alkyl)C(O)R^8, -CH=CH-R^8 and ;

R^8 is independently selected from
    hydrogen, unsubstituted or substituted C$_1$-C$_6$ alkyl,
    cycloalkyl, benzyl and unsubstituted or substituted aryl;

R^9 is independently selected from
    H, unsubstituted or substituted C$_1$-C$_6$ alkyl, benzyl and
    unsubstituted or substituted aryl;

R^{13} is independently selected from
    H, unsubstituted or substituted C$_1$-C$_6$ alkyl, unsubstituted
    or substituted aryl, unsubstituted or substituted heterocycle,
    -(C$_1$-C$_6$ alkyl)OR^8, -(C$_1$-C$_6$ alkyl)OC(O)(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$
    alkyl)N(R^8)$_2$, and -(C$_1$-C$_6$ alkyl)NHC(O)(C$_1$-C$_6$ alkyl)R^8;
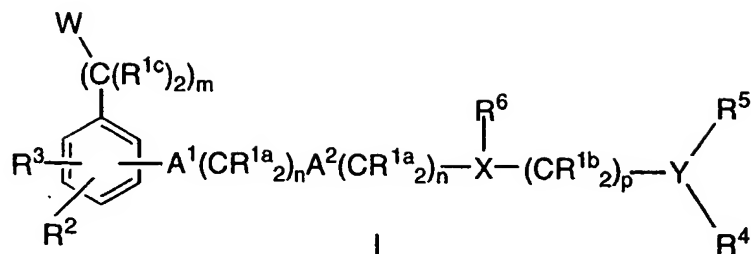
m is 0, 1, 2, 3 or 4;
n is   0, 1, 2, 3 or 4;
q is   0, 1 or 2; and
s is   0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

      9.   A compound of formula I:

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

5   a)   hydrogen,

         b)   unsubstituted or substituted aryl; unsubstituted or substituted heterocycle; unsubstituted or substituted heteroaryl; C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, or N_3;

10   c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or $R^8C(O)O$-;

15 R^2 is selected from:

         a)   hydrogen,

         b)   CN,

         c) NO_2,

         d)   halogen,

20   e)   aryl,

         f)   heteroaryl,

         g) C_1-C_6 alkyl,

         h) C_1-C_6 alkoxy,

         i) N_3,

25   j) $R^9S(O)_q$,

         k) $R^8C=C$, and

         l) $R^8C\equiv C$;

R^3, R^4 and R^5 are independently selected from:

a)   H,

b)   CN,

c) NO_2,

d)   halogen,

e) C_1-C_6 alkyl,

f) C_1-C_6 alkoxy,

g) N_3,

h) $R^9S(O)_q$,

i)   -$HC=CH_2$,

j)   -$C\equiv CH$,

k)   aryl, unsubstituted or substituted,

l)   heterocycle, unsubstituted or substituted,

m) CF_3O-,

n) CF_3CH_2O-,

o) C_3-C_{10} cycloalkyl, and

p) CF_3;

R^6 is independently selected from:

a)   hydrogen,

b)   CN,

c) NO_2,

d)   halogen,

e)   aryl, unsubstituted or substituted,

f)   heteroaryl, unsubstituted or substituted,

g) C_1-C_6 alkyl, unsubstituted or substituted,

h) R^8O,

i) N_3,

j) $R^9S(O)_q$,

k)   -$HC=CH_2$,

l)   -$C\equiv CH$,

m) CF_3

n) $R^8O(C=O)$, and

o) $R^8 (O=C)O$;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl, benzyl and aryl;

A^1 and A^2 are independently selected from:
- a) a bond,
- b) -HC=CH-,
- c) -C≡C-,
- d) O,
- e) $S(O)_q$,
- f) O(C=O),
- g) (O=C), and
- h) (C=O)O;

W is selected from:
- a)　　hydrogen,
- b)　　heterocycle, unsubstituted or substituted, and
- c)　　aryl, unsubstituted or substituted;

X is selected from:
- a)　　aryl,
- b)　　heteroaryl,
- c)　　cycloalkyl,
- d)　　heterocycle, and
- e)　　a bond;

Y is selected from:
- a)　　aryl, unsubstituted or substituted,
- b)　　heterocycle, unsubstituted or substituted, and
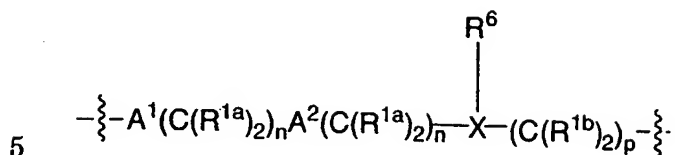- c)　　heteroaryl, unsubstituted or substituted;

m is　0, 1, 2, 3 or 4;

n is　0, 1, 2, 3 or 4;

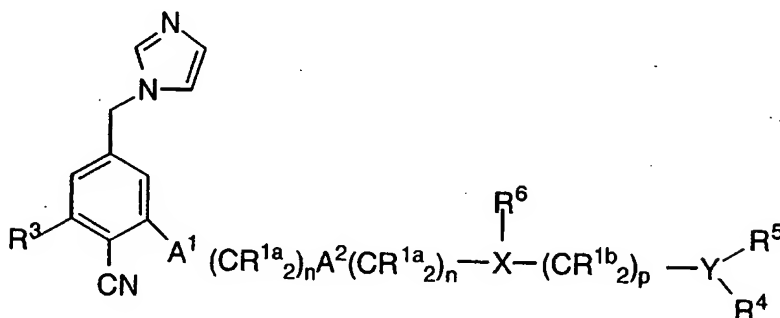p is   0, 1, 2, 3 or 4; and

q is   0, 1 or 2;

provided that

$$-\xi-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n\overset{\overset{\displaystyle R^6}{|}}{X}-(C(R^{1b})_2)_p-\xi-$$

is not a bond;

or the pharmaceutically acceptable salts thereof.

10. The compound of Claim 9, illustrated by formula Ia:

Ia

wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:
  a)   hydrogen,
  b)   aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O- or C_2-C_6 alkenyl,
  c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, or R^8O-;

R^3 and R^4 are independently selected from hydrogen, F, Cl, Br, N3, CN, C_1-C_6 alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

5   R^5 is selected from:

a) hydrogen, and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-

10   C_{10} cycloalkyl, CF_3, NO_2, R^8O-, $R^9S(O)_q$-, $R^8C(O)$-, $R^8OC(O)$-, N3, and CN;

R^6 is independently selected from:

a)   hydrogen,

15   b) C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, F, Cl, CN, NO_2, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)$-, or $R^8OC(O)$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and

20   aryl;

R^9 is independently selected from C_1-C_6 alkyl, benzyl and aryl;

A^1 and A^2 are independently selected from: a bond, -HC=CH-, -C≡C-, O,

25    $S(O)_q$, O(C=O), and (O=C)O;

X is selected from:

a)   aryl,

b)   heteroaryl,

30   c)   cycloalkyl,

d)   heterocycle, and

e)   a bond;

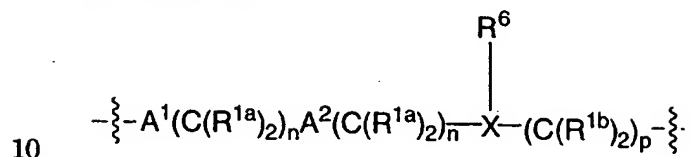Y is selected from:

35   a)   aryl,

b)   substituted aryl,

c)   heterocycle, and

d)   substituted heterocycle;

5.   n is   0, 1, 2, 3 or 4;

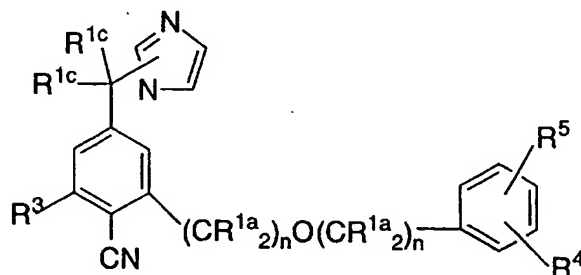p is   0, 1, 2, 3 or 4; and

q is   0, 1, or 2;

provided that

$$-\{-A^1(C(R^{1a})_2)_nA^2(C(R^{1a})_2)_n-X-(C(R^{1b})_2)_p-\}-$$

with R^6 on X

is not a bond;

or the pharmaceutically acceptable salts thereof.

11.   The compound of Claim 9, illustrated by formula Ib:

Ib

wherein:

20   R^{1a} is selected from:

a)   hydrogen,

b)   unsubstituted or substituted aryl; unsubstituted or
        substituted heterocycle; unsubstituted or substituted

heteroaryl; C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-, CN, NO_2, $R^8C(O)$-, $R^8OC(O)$-, or N_3;

    c) C_1-C_6 alkyl, unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_q$-,CN, $R^8C(O)$-, $R^8OC(O)$-, N_3, or -$R^8C(O)O$-;

R^{1c} is independently selected from: H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R^3 is selected from hydrogen, F, Cl, Br, N_3, CN, C_1-C_6 alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^4 and R^5 are independently selected from:
    a)   H,
    b)   halogen,
    c)   aryl, unsubstituted or substituted,
    d)   heteroaryl, unsubstituted or substituted, and
    e) C_1-C_6 alkyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl, benzyl and aryl;

n is independently selected from: 0, 1, 2, 3 or 4; and
q is   0, 1 or 2;

or the pharmaceutically acceptable salts thereof.

    12.   A compound which inhibits a prenyl-protein transferase, selected from the group consisting of:

3-(biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

3-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-ylmethylbenzonitrile

5

3-(biphenyl-3-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphenyl-4-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

10   2-(biphenyl-4-yl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

1-*tert*-butoxycarbonyl-4-(3-chlorophenyl)-2(S)-[2-(2-cyano-5-imidazol-1-
ylmethyl-phenoxy)ethyl]piperazine

15   2-(3-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

20

2-(2-chlorophenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(phenyl-2-ethoxy)-4-imidazol-1-ylmethyl-benzonitrile

25   2-(3-chlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-chlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dichlorobenzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

30

2-(benzyloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphenyl-2-ylmethoxy)-4-imidazol-1-ylmethyl-benzonitrile

35   2-(phenyl-4-butoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(phenyl-3-propoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphenyl-4-yl-2-ethoxy)-4-(1,2,4-triazol-1-yl)methyl-benzonitrile

5

2-(biphenyl-4-yl-2-ethoxy)-4-(2-methyl-imidazol-1-yl)methyl-benzonitrile

2-(biphenyl-4-yl-2-ethoxy)-4-benzimidazol-1-yl)methyl-benzonitrile

10   4-imidazol-1-ylmethyl-2-(naphthalen-2-yloxy)-benzonitrile

2-(3-cyanophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-bromophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

15

2-(biphen-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(biphen-4-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

20   2-(3-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-acetylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-trifluoromethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

25

2-(3-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

30   2-(4-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

35

2-(4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,5-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

5   2-(3,4-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,5-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(1-naphthyloxy)-4-imidazol-1-ylmethyl-benzonitrile

10

2-(2,4-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-fluorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

15   2-(3-t-butylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-[3-(N,N-diethylamino)phenoxy]-4-imidazol-1-ylmethyl-benzonitrile

2-(3-n-propylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

20

2-(2,3-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,3-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

25   2-(3,4-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,5-dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,4-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

30

2-(2,4-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-chloro-2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

35   2-(5-chloro-2-methylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chloro-4,5-dimethylphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(5-hydroxymethyl-2-methoxyphenoxy)-4-imidazol-1-ylmethyl-
benzonitrile

4-imidazol-1-ylmethyl-2-(3-phenylamino-phenoxy)-benzonitrile

4-imidazol-1-ylmethyl-2-[3-(2-methylphenylamino)-phenoxy]-benzonitrile

4-imidazol-1-ylmethyl-2-(3-phenoxy-phenoxy)-benzonitrile

2-(2-benzoyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

1-(5-chloro-2-methoxy-phenyl)-3-[3-(2-cyano-5-imidazol-1-ylmethyl-
phenoxy)-phenyl]-urea

1-(2,5-dimethoxy-phenyl)-3-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-
phenyl]-urea

2-(3-benzyloxy-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-benzyloxy-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-benzyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-ethynyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(4-acetyl-3-methyl-phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(1H-indazol-6-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(5,6,7,8-tetrahydro-naphthalen-1-yloxy)-
benzonitrile

4-imidazol-1-ylmethyl-2-(8-oxo-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-
benzonitrile

4-imidazol-1-ylmethyl-2-(1*H*-indol-7-yloxy)-benzonitrile

5

4-imidazol-1-ylmethyl-2-(3-oxo-indan-4-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(1*H*-indol-4-yloxy)-benzonitrile

10   2-[3-(2-hydroxy-ethoxy)-phenoxy]-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(4-imidazol-1-yl-phenoxy)-benzonitrile

4'-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-biphenyl-4-carbonitrile

15

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-acetamide

4-imidazol-1-ylmethyl-2-(9-oxo-9*H*-fluoren-4-yloxy)-benzonitrile

20   3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*phenyl-benzamide

3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-ethyl-*N*-phenyl-benzamide

3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-cyclopropylmethyl-*N*-
25   phenyl-benzamide

2-(5-chloro-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-
30   benzenesulfonamide

4-imidazol-1-ylmethyl-2-(indan-5-yloxy)-benzonitrile

3-(9*H*-carbazol-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

35

4-imidazol-1-ylmethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(2-methoxy-4-propenyl-phenoxy)-benzonitrile

5

4-imidazol-1-ylmethyl-2-[4-(3-oxo-butyl)-phenoxy]-benzonitrile

2-(3-chlorophenoxy)-5-imidazol-1-ylmethyl-benzonitrile

10   2-(4-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3,5-dichlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

15

2-(2-chlorophenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(3-chlorophenoxy)-5-(4-phenyl-imidazol-1-ylmethyl)-benzonitrile

20   2-(biphen-2-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(phenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chloro-4-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

25

2-(2-chlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile

4-imidazol-1-ylmethyl-2-(naphthalen-2-ylsulfanyl)-benzonitrile

30   2-(2,4-dichlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dichloro-benzenesulfinyl)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dichloro-benzenesulfonyl)-4-imidazol-1-ylmethyl-benzonitrile

35

2-(2-methyl-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2,4-dimethyl-pyridin-3-yloxy)-4-imidazol-1-ylmethyl-benzonitrile

5   2-(4-chloro-2-methoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

2-(2-chlorophenoxy)-4-(5-methyl-imidazol-1-ylmethyl)-benzonitrile

2-(2-chlorophenoxy)-4-(4-methyl-imidazol-1-ylmethyl)-benzonitrile

10

2-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-4-imidazol-1-ylmethyl-
benzonitrile

2-(2,4-dichlorophenoxy)-4-(2-methyl-imidazol-1-ylmethyl)-benzonitrile

15

N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-benzamide

2-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-N-phenyl-
acetamide

20

4-imidazol-1-ylmethyl-2-(quinolin-6-yloxy)-benzonitrile

4-imidazol-1-ylmethyl-2-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-benzonitrile

25   N-[3-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-phenyl]-2-phenyl-
acetamide

5-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-N-cyclohexyl-nicotinamide

30   N-(3-chloro-phenyl)-5-(2-cyano-5-imidazol-1-ylmethyl-phenoxy)-
nicotinamide

2-(2,3-dimethoxyphenoxy)-4-(2,4-dimethyl-imidazol-1-ylmethyl)-
benzonitrile

35

4-(2-methyl-imidazol-1-ylmethyl)-2-(naphthalen-2-yloxy)-benzonitrile

4-(1-imidazol-1-yl-1-methyl-ethyl)-2-(naphthalen-2-yloxy)-benzonitrile

5   1-[4-iodo-3-(naphthalen-2-yloxy)-benzyl]-1*H*-imidazole

acetic acid 3-[3-(2-chloro-phenoxy)-4-cyano-benzyl]-3H-imidazol-4-ylmethyl ester

10 2-(2-chloro-phenoxy)-4-(5-hydroxymethyl-imidazol-1-ylmethyl)-benzonitrile

4-(5-aminomethyl-imidazol-1-ylmethyl)-2-(2-chloro-phenoxy)-benzonitrile

15

N-{3-[4-cyano-3-(2,3-dimethoxy-phenoxy)-benzyl]-3H-imidazol-4-ylmethyl}-2-cyclohexyl-acetamide

2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-

20 benzonitrile

2-(3-chloro-phenoxy)-4-[1-(4-chloro-phenyl)-2-hydroxy-1-imidazol-1-yl-ethyl]-benzonitrile

25 2-(3-chloro-phenoxy)-4-[(4-chloro-phenyl)-hydroxy-(3*H*-imidazol-4-yl)-methyl]-benzonitrile

2-(2,4-dichloro-phenylsulfanyl)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-ylmethyl]-benzonitrile

30

2-(2,4-dichloro-phenoxy)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-ylmethyl]-benzonitrile

4-[hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-2-(naphthalen-2-yloxy)-

35 benzonitrile

4-[amino-(3-methyl-3*H*-imidazol-4-yl)-methyl]-2-(naphthalen-2-yloxy)-
benzonitrile

5   4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-
benzonitrile

4-[1-amino-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(naphthalen-2-yloxy)-
benzonitrile hydrochloride

10

3-{2-cyano-5-[1-amino-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-
ethyl-*N*-phenyl-benzamide

3-{2-cyano-5-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-phenoxy}-*N*-
15   ethyl-*N*-phenyl-benzamide

4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(3-phenylamino-
phenoxy)-benzonitrile

20   4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-2-(3-phenoxy-phenoxy)-
benzonitrile

2-(3-benzoyl-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-
benzonitrile

25

2-(3-*tert*-butyl-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-
ethyl]-benzonitrile

2-(3-diethylamino-phenoxy)-4-[1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-
30   ethyl]-benzonitrile

2-(5-chloro-2-oxo-2*H*-[1,2']bipyridinyl-5'-ylmethoxy)-4-imidazol-1-
ylmethyl-benzonitrile

4-Imidazol-1-ylmethyl-2-[2-(2-oxo-2H-pyridin-1-yl)-phenoxy]-benzonitrile

4-Imidazol-1-ylmethyl-2-[3-(2-oxo-2H- pyridin-1-yl)-phenoxy]-benzonitrile

5

4-Imidazol-1-ylmethyl-2-[4-(2-oxo-2H- pyridin-1-yl)-phenoxy]-benzonitrile

10 or the pharmaceutically acceptable salts thereof.

13. The compound according to Claim 12 which is:
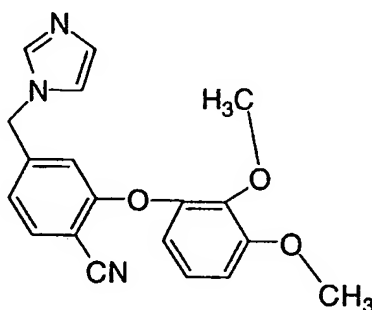
2-(2,3-Dimethoxyphenoxy)-4-imidazol-1-ylmethyl-benzonitrile

15

or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 12 which is:

20

4-Imidazol-1-ylmethyl-2-(naphthalen-2-yloxy)-benzonitrile

or a pharmaceutically acceptable salt thereof.

5   15.   The compound according to Claim 12 which is:

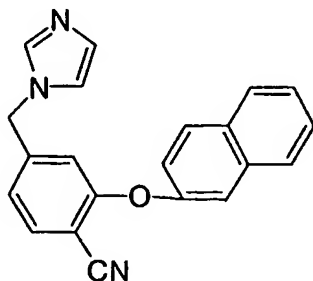2-(2,4-Dichlorophenylsulfanyl)-4-imidazol-1-ylmethyl-benzonitrile

10

or a pharmaceutically acceptable salt thereof.
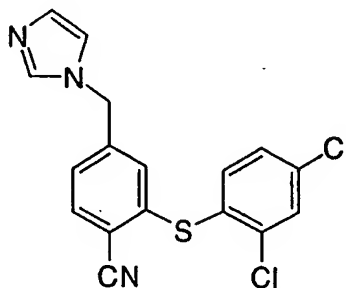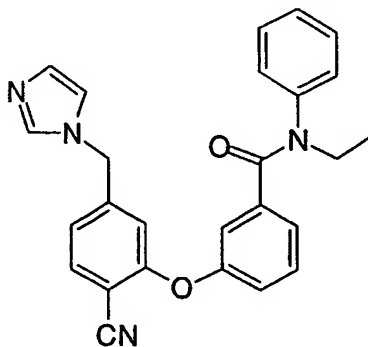
16.   The compound according to Claim 12 which is:

15

3-(2-Cyano-5-imidazol-1-ylmethyl-phenoxy)-*N*-ethyl-*N*-phenyl-benzamide

or a pharmaceutically acceptable salt thereof.

20

17.   The compound according to Claim 12 which is:
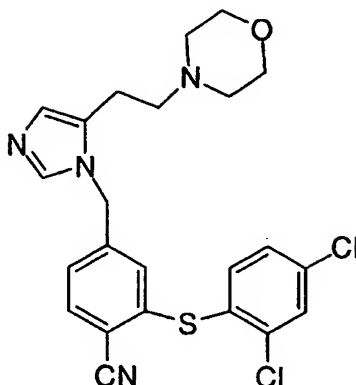
2-(2,4-dichloro-phenylsulfanyl)-4-[5-(2-morpholin-4-yl-ethyl)-imidazol-1-
5   ylmethyl]-benzonitrile

or a pharmaceutically acceptable salt thereof.

18.   A pharmaceutical composition comprising a
10   pharmaceutical carrier, and dispersed therein, a therapeutically
effective amount of a compound of Claim 1.

19.   A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically
15   effective amount of a compound of Claim 5.

20.   A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically
effective amount of a compound of Claim 12.
20

21.   A method for inhibiting a prenyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 18.

22. A method for inhibiting a prenyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 19.

23. A method for inhibiting a prenyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 20.

24. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

25. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 19.

26. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 20.

27. A method for treating neurofibromen benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

28. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

29. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

30.   A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

5   31.   A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

32.   A pharmaceutical composition made by combining
10   the compound of Claim 1 and a pharmaceutically acceptable carrier.

33.   A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

15

SEQUENCE LISTING

<110> deSolms, S. Jane
        Hutchinson, John H.
        Shaw, Anthony W.
        Graham, Samuel L.
        Ciccarone, Terrence M.
        Merck & Co., Inc.

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Cys Leu Ile Met
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        <210> 11
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        <400> 11
Cys Val Leu Ser
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Cys Ala Ile Leu
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 1               5                   10                  15
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        <211> 86
        <212> DNA
        <213> Artificial Sequence

        <220>
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        <400> 14
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gatgacagaa tacaagcttg tggtgg                                            86
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        <211> 33
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    <212> DNA
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    <212> DNA
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    <220>
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    <400> 17
cactctagac tggtgtcaga gcagcacaca cttgcagc                                   38

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    <211> 38
    <212> DNA
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    <220>
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    <400> 18
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    <210> 19
    <211> 33
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    <220>
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gagagaattc gccaccatga ctgagtacaa actggtgg   38

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<213> Artificial Sequence

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<210> 23
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<220>
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<400> 23
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<213> Artificial Sequence

<220>
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<400> 24
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       <220>
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       <210> 26
       <211> 24
       <212> DNA
       <213> Artificial Sequence

       <220>
       <223> completely synthesized

       <400> 26
gtagttggag ctgttggcgt aggc   24

INTERNATIONAL SEARCH REPORT

	International application No.
	PCT/US98/21063

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6)   :Please See Extra Sheet.
US CL   :514/235.8, 341, 399; 544/139; 546/275.1; 548/336.1
According to International Patent Classification (IPC) or to both national classification and IPC

B.   FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S.   :   548/336.1; 546/275.1; 544/139; 514/235.8, 341, 399

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C.   DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,690,942 A (FRICK et al.) 01 September 1987, see entire document.	1-33
A	US 5,559,141 A (KARJALAINEN et al.) 24 September 1996, see entire document.	1-33
X,P	US 5,780,492 A (DINSMORE et al.) 14 July 1998. see entire document.	1-6, 18, 19, 21, 22, 24, 25, 27-33

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 DECEMBER 1998	2 6 JAN 1999

Name and mailing address of the ISA/US	Authorized officer
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A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6): A61K 31/535, 31/44, 31/415; C07D 413/00, 401/00, 417/00, 419/00, 233/66

B. FIELDS SEARCHED
Documentation other than minimum documentation that are included in the fields searched:

Chemical Abstracts
Index Chemicus
Current Abstracts of Chemistry